Treatment of periodontitis for glycaemic control in people with diabetes mellitus

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Treatment of periodontitis for glycaemic control in people with diabetes mellitus.
Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No.: CD004714.
DOI: 10.1002/14651858.CD004714.pub4.

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[Intervention Review]

Treatment of periodontitis for glycaemic control in people with diabetes mellitus

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Editorial group: Cochrane Oral Health Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 4, 2022.

Citation: Simpson TC, Clarkson JE, Worthington HV, MacDonald L, Weldon JC, Needleman I, Iheozor-Ejiofor Z, Wild SH, Qureshi A, Walker A, Patel VA, Boyers D, Twigg J.Treatment of periodontitis for glycaemic control in people with diabetes mellitus. *Cochrane Database of Systematic Reviews* 2022, Issue 4. Art. No.: CD004714. DOI: 10.1002/14651858.CD004714.pub4.

ABSTRACT

Background

Glycaemic control is a key component in diabetes mellitus (diabetes) management. Periodontitis is the inflammation and destruction of the underlying supporting tissues of the teeth. Some studies have suggested a bidirectional relationship between glycaemic control and periodontitis.

Treatment for periodontitis involves subgingival instrumentation, which is the professional removal of plaque, calculus, and debris from below the gumline using hand or ultrasonic instruments. This is known variously as scaling and root planing, mechanical debridement, or non-surgical periodontal treatment. Subgingival instrumentation is sometimes accompanied by local or systemic antimicrobials, and occasionally by surgical intervention to cut away gum tissue when periodontitis is severe.

This review is part one of an update of a review published in 2010 and first updated in 2015, and evaluates periodontal treatment versus no intervention or usual care.

Objectives

To investigate the effects of periodontal treatment on glycaemic control in people with diabetes mellitus and periodontitis.

Search methods

An information specialist searched six bibliographic databases up to 7 September 2021 and additional search methods were used to identify published, unpublished, and ongoing studies.

Selection criteria

We searched for randomised controlled trials (RCTs) of people with type 1 or type 2 diabetes mellitus and a diagnosis of periodontitis that compared subgingival instrumentation (sometimes with surgical treatment or adjunctive antimicrobial therapy or both) to no active intervention or 'usual care' (oral hygiene instruction, education or support interventions, and/or supragingival scaling (also known as

PMPR, professional mechanical plaque removal)). To be included, the RCTs had to have lasted at least 3 months and have measured HbA1c (glycated haemoglobin).

Data collection and analysis

At least two review authors independently examined the titles and abstracts retrieved by the search, selected the included trials, extracted data from included trials, and assessed included trials for risk of bias. Where necessary and possible, we attempted to contact study authors.

Our primary outcome was blood glucose levels measured as glycated (glycosylated) haemoglobin assay (HbA1c), which can be reported as a percentage of total haemoglobin or as millimoles per mole (mmol/mol).

Our secondary outcomes included adverse effects, periodontal indices (bleeding on probing, clinical attachment level, gingival index, plaque index, and probing pocket depth), quality of life, cost implications, and diabetic complications.

Main results

We included 35 studies, which randomised 3249 participants to periodontal treatment or control. All studies used a parallel-RCT design and followed up participants for between 3 and 12 months. The studies focused on people with type 2 diabetes, other than one study that included participants with type 1 or type 2 diabetes. Most studies were mixed in terms of whether metabolic control of participants at baseline was good, fair, or poor. Most studies were carried out in secondary care.

We assessed two studies as being at low risk of bias, 14 studies at high risk of bias, and the risk of bias in 19 studies was unclear. We undertook a sensitivity analysis for our primary outcome based on studies at low risk of bias and this supported the main findings.

Moderate-certainty evidence from 30 studies (2443 analysed participants) showed an absolute reduction in HbA1c of 0.43% (4.7 mmol/mol) 3 to 4 months after treatment of periodontitis (95% confidence interval (CI) -0.59% to -0.28%; -6.4 mmol/mol to -3.0 mmol/mol). Similarly, after 6 months, we found an absolute reduction in HbA1c of 0.30% (3.3 mmol/mol) (95% CI -0.52% to -0.08%; -5.7 mmol/mol to -0.9 mmol/mol; 12 studies, 1457 participants), and after 12 months, an absolute reduction of 0.50% (5.4 mmol/mol) (95% CI -0.55% to -0.45%; -6.0 mmol/mol to -4.9 mmol/mol; 1 study, 264 participants).

Studies that measured adverse effects generally reported that no or only mild harms occurred, and any serious adverse events were similar in intervention and control arms. However, adverse effects of periodontal treatments were not evaluated in most studies.

Authors' conclusions

Our 2022 update of this review has doubled the number of included studies and participants, which has led to a change in our conclusions about the primary outcome of glycaemic control and in our level of certainty in this conclusion. We now have moderate-certainty evidence that periodontal treatment using subgingival instrumentation improves glycaemic control in people with both periodontitis and diabetes by a clinically significant amount when compared to no treatment or usual care. Further trials evaluating periodontal treatment versus no treatment/usual care are unlikely to change the overall conclusion reached in this review.

PLAIN LANGUAGE SUMMARY

Does treatment for gum disease help people with diabetes control blood sugar levels?

Review question

The main question addressed by this review is: how effective is gum disease (periodontitis) treatment for controlling blood sugar levels (known as glycaemic control) in people with diabetes, compared to no active treatment or usual care?

Background

The aim of treating periodontitis is to reduce swelling and infection and stabilise the condition of the gums and supporting bone. The level of sugar in the blood is too high in people with diabetes, so keeping blood sugar levels under control is a key issue. Some clinical research suggests a relationship exists between gum disease treatment and glycaemic control.

Glycaemic control can be measured in different ways. For this review, we focused on HbA1c, which shows average blood glucose levels over the preceding 3 months. It can be reported as a percentage (of total haemoglobin) or as mmol/mol (millimoles per mole). Excellent glycaemic control in a diabetic person might be around 6.5% or 48 mmol/mol.

This review was carried out by authors working with the Cochrane Oral Health and is part one of an update of a review previously published in 2010 and 2015. This review evaluates gum disease treatment versus no active treatment or usual care. Part two of the review will compare different types of periodontal treatment. We carried out this review as it is important to discover if gum disease treatment does improve glycaemic control in order to ensure best use of clinical resources.

Study characteristics

We searched six research databases and found 35 relevant trials where people with diabetes and periodontitis were randomly allocated to an experimental group or a control group. The experimental groups received gum disease treatment called 'subgingival instrumentation', also known as scaling and root planing or deep cleaning. In some experimental groups, the deep cleaning was supplemented with instructions for cleaning teeth properly ('oral hygiene instruction'), or other gum treatments, for example, antimicrobials, which are used to treat infections. Control groups received no active treatment or 'usual care', which was oral hygiene instruction, support with oral hygiene, and/or removal of plaque above the gumline.

The trials randomised 3249 participants in total. Almost all participants had type 2 diabetes, with a mix of good, fair, and poor diabetic control. Most of the studies were carried out in hospitals. The studies followed up participants for between 3 and 12 months.

Key results

Evidence from 30 trials (results from 2443 participants) showed that periodontitis treatment reduces blood sugar levels (measured by HbA1c) in diabetic patients on average by 0.43 percentage points (e.g. from 7.43% to 7%; 4.7 mmol/mol) 3 to 4 months after receiving the treatment compared with no active treatment or usual care. A difference of 0.30% (3.3 mmol/mol) was seen after 6 months (12 studies), and 0.50% (5.4 mmol/mol) at 12 months (one study).

There were not enough studies measuring side effects to be able to evaluate the risk of harm from gum disease treatments.

Certainty of the evidence

Most of the studies were conducted in a way that meant they were at a high risk of bias or did not provide enough information for us to make a judgement on this. However, the consistency of our findings suggests they are reliable and future research is not likely to change them.

In summary, currently there is moderate-certainty evidence to support gum disease treatment (known as subgingival instrumentation) for controlling blood sugar levels in people with periodontitis (gum disease) and diabetes up to 12 months after the start of the periodontal treatment.

Date of the search

The evidence is current up to 7 September 2021.

Summary of findings 1. Periodontal treatment compared to no treatment/usual care for glycaemic control in people with diabetes mellitus

Periodontal treatment versus no active treatment/usual carefor glycaemic control in people with diabetes mellitus					
Population: people with diabetes mellitus and periodontitis **Settings:** hospital, primary care, community **Intervention:** periodontal treatment **Comparison:** no active treatment/usual care					
Outcomes	**Illustrative comparative risks* (95% CI)**		**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**			
	Usual care/no active treatment	**Periodontal treatment**			
HbA1c Follow-up: 3 to 4 months	The median HbA1c at 3 to 4 months follow-up was 7.74%	The mean HbA1c in the periodontal treatment groups was **0.43 percentage points lower** (95% CI 0.28 to 0.59 lower)[c]	2443 (30 studies (4 with multiple arms))	⊕⊕⊕⊖ **MODERATE**[a,b]	Periodontal treatment probably improves glycaemic control as measured by HbA1c at 3 to 4 months follow-up. Results in favour of periodontal treatment were also found at 6 and 12 months (6 months: -0.30%, 95% CI -0.52% to -0.08%; I^2 = 80%; 12 studies, 1457 participants; 12 months: -0.50%, 95% CI -0.55% to -0.45%; 1 study, 264 participants)[d]
Adverse effects	Insufficient evidence to determine whether SRP for glycaemic control is associated with any harms. Most studies did not evaluate adverse effects				

*The **assumed risk** is the mean control group risk across studies. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **HbA1c:** glycated haemoglobin; **mmol/mol:** millimoles per mole; **SRP:** scaling and root planing

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level for high risk of bias, largely due to lack of blinding.
[b]Not downgraded for moderate heterogeneity (I^2 = 70%) at 3 to 4 months because of similar effects seen across all time periods.
[c]Mmol/mol equivalent: 4.7 mmol/mol lower in the intervention group than the control group after 3 to 4 months (95% CI -6.4 to -3.0).

[d]Mmol/mol equivalents: 3.3 mmol/mol lower in the intervention group than the control group after 6 months (95% CI -5.7 to -0.9), and 5.4 mmol/mol lower in the intervention group than the control group after 12 months (95% CI -6.0 to -4.9).

BACKGROUND

Description of the condition

Diabetes mellitus

Diabetes mellitus (DM) is a chronic metabolic disease that is caused by the body's failure either to produce the hormone insulin or to effectively use its production of insulin. Insulin is a hormone produced by the pancreas that enables the body to direct glucose from the bloodstream to cells for energy. Without this vital hormone, glucose accumulates in the bloodstream and can result in disabling and life-threatening complications.

In 2014, the global prevalence of DM was estimated to be 8.5% among adults over 18 years old (WHO 2015). In 2021, the global diabetes prevalence in 20- to 79-year olds was estimated to be 10.5% (536.6 million people), with similar prevalence among men and women, and highest prevalence in those aged 75 to 79 years (International Diabetes Federation 2021; Sun 2021); and predictions this will rise to 12.2% (783.2 million) in 2045. In 2019, diabetes was reported to be the ninth leading cause of death with an estimated 1.5 million deaths directly attributable to diabetes (WHO 2021). In 2011, under the leadership of the World Health Organization (WHO), governments agreed a global action plan for the prevention and control of non-communicable diseases, with a target of reducing global premature deaths in the 30- to 70-year-old age group by 25% by 2025 as part of its overall strategy (WHO 2013; WHO 2014).

The cost to governmental health budgets of managing people with diabetes is substantial. The global cost of diabetes care in 2021 was estimated to be USD 612 billion (International Diabetes Federation 2013). The spending on diabetes-related disease has been found to be positively associated with the gross domestic product of countries (Seuring 2015). The economic burden on the UK was estimated to be approximately GBP 9.8 billion in 2010/11 or 10% of the National Health Service (NHS) budget, with GBP 8.8 billion of this amount relating to treatment for people with type 2 diabetes mellitus, and a further projected rise to 17% of health service resources by 2035/2036 (Hex 2012).

Glycaemic control is a key component in DM management. Prolonged hyperglycaemia is associated with complications including retinopathy, peripheral neuropathy, macrovascular disease (coronary heart and cerebrovascular disease), foot disease (arising from a combination of vascular and neuropathic disease), and renal failure. The United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications trial in the USA have demonstrated that intensive treatment of hyperglycaemia can reduce the risk of long-term complications (DCCT 1993; Stratton 2000; UKPDS 1998). Each absolute reduction of 1% in haemoglobin A1c (HbA1c) in the UKPDS was associated with a relative risk reduction of 21% for any diabetes-related endpoint, 21% for diabetes-related deaths, 14% for myocardial infarction, and 37% for microvascular complications (Stratton 2000). As part of this process, blood glucose levels may be monitored daily by the patient, but also by regular haematological tests in a clinical laboratory. The HbA1c level is commonly measured to assess blood glucose levels over a period of approximately 6 to 8 weeks preceding the test and is recognised as a good indicator of glycaemic control, particularly as higher HbA1c levels are associated with an increased risk of diabetes-related complications (Bunn 1981).

A number of different blood indices have been identified as indicators of blood glucose levels and therefore possible prognostic markers. The glycated (glycosylated) haemoglobin assay (HbA1c) gained widespread acceptance during the 1980s as the laboratory test of choice and is still widely used. HbA1c has been measured using a number of differing methods with several internationally adopted standards. These include the Diabetes Control and Complications Trial (DCCT) or the International Federation of Clinical Chemistry (IFCC) standard tests (their respective standardised values were implemented globally after achieving consensus in 2007 before being refined further in 2009 (Hanas 2010)). The latter consistently gives lower values (non-diabetic reference range is about 3% to 5% IFCC and 4% to 6% DCCT), with good control in diabetic groups as 5% IFCC and 7% DCCT. Treatment alteration becomes a requirement with values > 6% IFCC and > 8% DCCT (Florkowski 2003).

In most of Europe, HbA1c has been expressed using the units mmol/mol, in accordance with the International Federation of Clinical Chemistry (IFCC) reference measurement procedure (Hanas 2010). However, many clinicians and scientists in the UK, USA, and other countries worldwide have been slower to transition from percentage (%) units previously in use. Most studies evaluated expressed HbA1c as % units. We have used percentages throughout the review, and have added the millimoles per mole (mmol/mol) equivalents for the main results. It should be noted that when referring to percentage reductions in HbA1c throughout this review, this refers to absolute reductions (e.g. an absolute reduction of 1% in HbA1c would be represented by a change from 8% to 7%).

Some studies measure blood glucose levels such as plasma glucose fasting levels. Although blood glucose is useful for management on a daily basis (particularly in type 1 DM), we do not think it is an appropriate measure to use as it can be very variable and be heavily influenced by many factors, such as diet and exercise. HbA1c gives a better measure of long-term glycaemic control and has been shown to be more strongly associated with complications of diabetes than blood glucose (Goldstein 2004; Karnchanasorn 2016).

While achieving good glycaemic control is the focus of this review, it should be noted that it is only one component of management of diabetes; smoking cessation, weight loss, physical activity, and management of dyslipidaemia and hypertension, where appropriate, are particularly important to reduce risk of macrovascular disease.

Periodontitis

Poorly controlled diabetes is a recognised risk factor for developing periodontitis (D'Aiuto 2017; Papapanou 1996; Preshaw 2012; Seppälä 1993; Tonetti 2018). There is epidemiological evidence that people with both type 1 diabetes mellitus (T1DM) and type 2 (T2DM) experience periodontitis more frequently, and with a greater severity, than the general population (Firatli 1997; Sandberg 2000).

Periodontitis is defined as inflammation and destruction of the underlying supporting tissues of the teeth (the periodontium) as a chronic multifactorial inflammatory disease associated with dysbiotic plaque biofilms and characterised by progressive

destruction of the tooth-supporting apparatus (Papapanou 2018). In susceptible patients whose oral hygiene is suboptimal, a microbial biofilm (bacteria and extracellular substances) can form around the gingival margin and result in inflammation and destruction of the periodontium (Abusleme 2021). This complex, chronic disease requires lifelong control of the causative factors (Kornman 2014; Sanz 2020). Reduced periodontal support can lead to mobility (or drifting) of teeth, and ultimately tooth loss; this in turn may require additional treatment to restore lost function and appearance. It has been estimated that the total surface area of inflamed and ulcerated epithelium of the periodontal tissues in an individual with periodontitis is at least equivalent to the surface area of the palm of the hand (Page 1998). Chronic inflammation of the periodontium may also contribute to systemic inflammation more distantly (Hajishengallis 2021; Schenkein 2020).

A new classification of periodontitis was proposed in 2017 (Caton 2018), with a unified classification for periodontitis that recognised the lack of evidence for different disease entities (such as previous differentiation between chronic and aggressive periodontitis) (Papapanou 2018). Periodontitis severity is classified as stages I, II, III, or IV by measurement of clinical attachment levels (clinical attachment loss, pocket depth, or both if available). Furthermore, the International Workshop for the first time defined periodontal heath and gingivitis with “case definitions primarily predicated on the presence of absence of bleeding on probing” with gingival health defined as < 10% bleeding sites with probing depths less than or equal to 3 mm (Chapple 2018).

While recognising that hyperglycaemia may affect dental plaque-induced diseases of the periodontium, the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions (workgroup 3) determined that “diabetes-associated periodontitis should not be regarded as a distinct diagnosis, but diabetes should be recognised as an important modifying factor and included in a clinical diagnosis of periodontitis as a descriptor” (Jepsen 2018). Within the classification, diabetes is recognised as one of only two risk factors with sufficient evidence to support that description (the other being tobacco use).

In previous years, evidence has been published suggesting a bidirectional relationship between glycaemic levels and periodontitis (D'Aiuto 2017; Grossi 1998; Stewart 2001; Taylor 2001). In other words, the chronic inflammation and infection that results from periodontitis could also have an adverse effect on glycaemic control in people with diabetes, while the impact of diabetes on immune function and inflammatory pathways could lead to negative effects on periodontal health. Authoritative trials on DM treatment such as DCCT 1993, Stratton 2000 and UKPDS 1998, and subsequent trials and population-based studies of people with diabetes have not collected data on periodontitis or oral health in general.

Observational studies have noted associations between socioeconomic status (SES broadly includes ethnicity, income, social class, and education) variables and periodontitis progression (low education and low income: Buchwald 2013), and SES (low income) and DM prevalence (Rabi 2006). This is therefore an important confounder that is difficult to account for reliably in observational study designs, supporting the need for randomised controlled trials.

Description of the intervention

Treatment of periodontitis involves sequenced steps of care (Sanz 2020). Step one includes oral hygiene instruction to educate and motivate people to control dental plaque and bacterial biofilm accumulation, the causative agent of periodontitis, in combination with professional mechanical plaque removal (PMPR).

The second step involves mechanical debridement by a dentist (generalist or specialist) or dental hygienist using hand or powered instruments or both to remove subgingival biofilm and calculus. This stage of treatment has historically been termed 'scaling and root planing', reflecting the goal of producing smooth, glassy cementum, which was thought to reduce the likelihood of reformation of microbial deposits. However, excessive planing is now known to be destructive to the tooth tissue and can result in a high incidence of complications, with no additional benefit over a less invasive approach to removal of deposits on the tooth roots. We have avoided using the term 'scaling and root planing' in the review, though most studies use this term. Instead we refer to this phase of treatment as 'subgingival instrumentation', in keeping with the latest S3 treatment guidelines by the European Federation for Periodontology (Sanz 2020).

With more advanced forms of disease, a third step may be required, including surgery to facilitate access to subgingival areas. Typically, surgery is reserved for a select number of sites in otherwise disease-stable patients with excellent oral hygiene, and is conducted by periodontists. Some of these measures require several visits. Where infection cannot be treated by these means, extraction may be recommended to achieve health and reduce the systemic effect of ongoing uncontrolled disease.

Antimicrobials (including antiseptics such as chlorhexidine and both systemic and locally delivered antibiotics) have also been used as adjuncts to subgingival instrumentation. However, there is no indication for the routine use of such adjuncts since the evidence of benefit is unclear (Sanz 2020).

Surgical treatment was not considered as a separate intervention to subgingival instrumentation in this review. Surgery is typically undertaken following an initial course of subgingival instrumentation, is reserved for specific sites in patients who otherwise have a good level of disease control following initial therapy, and aims to facilitate access to root surfaces to better achieve subgingival instrumentation, thus is not mechanistically different to non-surgical treatment.

It has been recommended that there should be integration of medical and dental care pathways to assist people who have been diagnosed with diabetes to seek assessment of their periodontal health and to provide effective treatment of periodontitis should this be present (NHS 2019; Sanz 2018).

How the intervention might work

Periodontitis results not only in local inflammation within the periodontal tissues but also leads to a systemic inflammatory response. Increasingly, inflammation is recognised as a cause of insulin resistance and therefore reducing systemic inflammation might lead to improvements in glycaemic control (D'Aiuto 2017). Treating periodontitis aims to remove subgingival calculus and plaque biofilm, which may enable healing to occur, reducing the size of periodontal pockets, which are considered as the primary

niche of disease-causing micro-organisms. Intensive treatment of periodontitis has been shown to result in a reduction in markers of systemic inflammation including C-reactive protein (CRP), and this is also correlated with improved periodontal health including reductions in pocket depths and bleeding on probing (Sanz 2018). People with both diabetes and periodontitis have been found to have higher levels of systemic inflammatory markers compared with people with periodontitis only, and treatment of periodontitis has been shown to result in a greater reduction in systemic inflammatory markers in people with diabetes compared with systemically healthy periodontitis patients (Preshaw 2020).

Any improvement in glycaemic control resulting from regular and appropriate periodontal treatment has the potential to make an impact on the development of diabetic complications and on quality of life for people with diabetes. There is debate around what should be considered a minimal clinically important reduction in HbA1c, and it has been proposed that this varies depending on the baseline value. To put this in context, the epidemiological analysis of UKPDS 1998 data indicated that for every percentage point decrease in HbA1c, there was a 35% reduction in the risk of microvascular complications, which appeared to be linear, though a linear relationship may not exist at lower levels. In a general population, of whom only a minority had diabetes, a lower average HbA1c level by 0.2% was associated with a 10% lower mortality over 2 to 5 years (Khaw 2001), although we acknowledge that the findings of this and other observational studies of people with diabetes are prone to confounding. Another approach to understanding clinical relevance of changes in HbA1c can be to compare to the effect of adding a second hypoglycaemic drug when treating people with diabetes. Typically, this results in an absolute reduction in HbA1c of 0.4% to 0.9% and therefore this range might represent a useful guide to interpreting trial results (Monami 2008).

Why it is important to do this review

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles (Worthington 2015). This review was identified as a priority title by the periodontal expert panel. In 2020, an updated prioritisation process was run and once again this review was identified as a priority. This is an update of the Cochrane Review published in 2010 and first updated in 2015 (Simpson 2010; Simpson 2015).

The 2015 version of this review concluded that periodontal treatment may be able to deliver an absolute reduction in HbA1c of 0.29% compared with usual care or no intervention when measured 3 to 4 months after the intervention, but found no evidence for an impact at 6 months. The studies could provide only evidence that we considered 'low certainty', which meant that future research was quite likely to change the findings. As many more studies have been conducted since 2015, we wanted to update the review to see whether the addition of new evidence would lead us to the same or different conclusions and whether it would give us more or less certainty in our findings. We were also interested in whether the type of studies being conducted had changed; for example, whether more studies had involved people with type 1 diabetes. In addition, we have worked with the National Institute for Health and Care Excellence (NICE) to provide up-to-date evidence to support the development of updated clinical guidelines on diabetes management. Due to the high number of trials that have been published since the last update of the review, we opted to divide our review update into two sections. This review (part 1) focuses on periodontal treatment versus usual care, while part 2 will be completed later this year and focuses on head-to-head comparisons of one periodontal treatment against another.

If periodontal treatments for people with diabetes can be shown to improve glycaemic control (reduced Hba1c), then additional costs of early preventative intervention may be offset by a reduction in complex episodes of care required to manage the long-term costs of diabetes-related complications. Similarly, if interventions can control periodontitis, slowing progression, then additional savings might be expected due to reduced need for referral to secondary dental care settings, and reduced costs associated with the long-term management of more advanced periodontitis. The net cost impact to healthcare payers (governments, insurers, and patient co-payments) of increased investment in effective preventative periodontal care and reduced long-term diabetes and periodontitis costs could be considerable (NHS 2019).

Policy makers require thorough economic evaluations to understand the long-term costs and consequences of investing in periodontal treatments for patients with diabetes. Whilst effective interventions might be expected to lead to long-term cost savings and cost-effectiveness, economic evaluations can elucidate the specific treatments and magnitude of effectiveness required to demonstrate cost-effectiveness. Decision-makers can then consider the costs of delivering and the effectiveness of various periodontal treatments in the broader context of longer term and indirect cost savings that might be achieved from improving diabetes or periodontitis control beyond the duration of follow-up in clinical trials. Incorporating a range of stakeholder perspectives (healthcare payers, diabetes and periodontitis patients, dental care providers, and society) ensures that policy makers have access to the most reliable information to make resource allocation decisions. The brief economic commentary (BEC) we conducted alongside this review summarises the current available cost-effectiveness evidence.

OBJECTIVES

To investigate the effects of periodontal treatment on glycaemic control in people with diabetes mellitus and periodontitis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs). We excluded trials if the participants were followed up for less than 90 days after completion of the treatment course. We excluded split-mouth and cross-over studies, due to the anticipated influence of carry-over effects from treatment.

Types of participants

We included studies of people with diabetes mellitus (DM) and periodontitis who were at least 16 years of age.

Diabetes diagnoses included type 1 (juvenile-onset diabetes or insulin-dependent DM (IDDM)), and type 2 (adult-onset or non-insulin dependent DM (NIDDM)).

For periodontitis, we accepted trialist statements that participants were selected on the basis of a diagnosis of periodontitis, including previous classifications such as chronic or adult periodontitis.

We included studies regardless of the general medical health of the participants; however, we would have excluded studies if more than 10% of the study sample had been diagnosed with gestational diabetes (diabetes associated with pregnancy) or if participants had metabolic syndrome.

No restriction was placed on setting - primary care, hospital, or community were all considered.

Types of interventions

Periodontitis treatment (any professionally-delivered intervention designed to reduce periodontitis) includes:

- subgingival instrumentation (also known as scaling and root planing, mechanical debridement, or non-surgical periodontal treatment).

It may also include one or more of the following:

- surgical periodontitis treatment - flap surgery or gingivectomy;
- antimicrobial therapy (encompassing antibacterials and antibiotics), either locally applied (including mouthrinses, 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;
- supragingival scaling (also known as professional mechanical plaque removal (PMPR));
- oral hygiene instruction;
- education or support sessions to improve self-help or self-awareness of oral hygiene.

We compared periodontitis treatment with control, which could be no (or delayed) treatment or usual care (oral hygiene instruction (OHI) or supragingival scaling with or without OHI).

Types of outcome measures

Primary outcomes

- Glycaemic control measured by HbA1c (glycated (glycosylated) haemoglobin assay), which can be reported as a percentage of total haemoglobin or as millimoles per mole (mmol/mol).

We excluded trials with less than 3-month follow-up duration due to human red blood cells ordinarily having a lifespan of between 8 to 12 weeks (Franco 2012).

We excluded trials that did not measure HbA1c as an outcome.

Secondary outcomes

- Clinical attachment level (CAL).
- Probing pocket depth (PPD).
- Bleeding on probing (BOP).
- Gingival indices (GI).
- Plaque indices (PI).
- Any adverse effects of treatment.
- Quality of life (e.g. OHIP-14 questionnaire).
- Diabetic complications.
- Cost implications.

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 7 September 2021);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 8) in the Cochrane Library (searched 7 September 2021);
- MEDLINE Ovid (1946 to 7 September 2021);
- Embase Ovid (1980 to 7 September 2021);
- CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1937 to 7 September 2021);
- LILACS BIREME Virtual Health Library (Latin American and Caribbean Health Science Information database; from 1982 to 7 September 2021).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategies designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions*, Version 6.1 (Lefebvre 2020)).

All the search strategies used can be found in Appendix 1.

Searching other resources

Cochrane Oral Health's Information Specialist searched the following databases for conference proceedings (see Appendix 1 for the search strategies):

- Web of Science via Clarivate Analytics (limited to conference proceedings) (1990 to 7 September 2021);
- ZETOC (zetoc.jisc.ac.uk, limited to conference proceedings) (1993 to 7 September 2021).

The following trial registries were searched for ongoing studies (see Appendix 1 for the search strategies):

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov; searched 7 September 2021);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 7 September 2021).

For previous versions of this review, we attempted to contact known authorities, as identified by the Cochrane Oral Health, in the following languages for information about publications, which might contain relevant trials: Japanese, Chinese, German, French, and Spanish. In addition to this, any papers we identified by any of the database searches that were in a language other than English were translated and considered for inclusion.

We contacted authors of relevant studies for clarification regarding their own studies and for information regarding other studies of which they were aware.

We handsearched the following journals for previous versions of this review:

- *Annals of Periodontology* (1996 to 2003);
- *Periodontology 2000* (1993 to 2003).

We did not handsearch any medical or specialist journals relating to diabetes. The handsearching was discontinued after 2003 due to poor yield.

We searched the reference lists of included studies and relevant systematic reviews for further studies.

We checked that none of the included studies in this review were retracted due to error or fraud.

We did not perform a separate search for adverse effects of interventions used, we considered adverse effects described in included studies only.

We performed a separate search to look for economic evaluations - see the 'Incorporating economic evidence' section below.

Data collection and analysis

Selection of studies

Two review authors screened all titles (and abstracts if available) in duplicate. The search was designed to be sensitive and include controlled clinical trials, these were filtered out early in the selection process if they were not randomised. We rejected clearly irrelevant records at this stage. We retrieved and examined the full text of potentially relevant studies. Four teams of two review authors independently extracted data in duplicate. Where authors disagreed on studies for inclusion, another review author acted as arbiter. The review authors were not blinded to the authors of the studies (which has been shown to be unnecessary (Berlin 1997)).

Data extraction and management

We used a pre-designed template to collect the following data from included studies:

- general characteristics - year of study, language of original publication, country of origin, and funding;
- trial design - sample size, method of allocation, blinding and comparative group characteristics;
- population studied - ethnic groups, setting, social class, whether type 1or type 2 diabetes (or both), further information on diagnosis, duration of diabetes, duration of diabetic control, level of diabetic control, other stated medical conditions, type of periodontitis, smoking habits, alcohol consumption, and drug therapy;
- nature of the intervention - oral hygiene, self-administered measures, type of periodontal treatment and antimicrobial/antiseptics employed, and adherence;
- primary outcomes - HbA1c at baseline, during treatment and post-treatment (and where available: test method, reference values, and corresponding DCCT (Diabetes Control and Complications Trial)/IFCC (International Federation of Clinical Chemistry) standards);
- secondary outcomes - changes in clinical attachment level (CAL), probing pocket depth (PPD), bleeding on probing (BOP), gingival index (GI) and plaque index (PI), diabetic complications, changes in antidiabetic therapy, and costs.

Two review authors extracted numerical data from the studies into data tables and Review Manager (RevMan) software (Review Manager 2020).

Assessment of risk of bias in included studies

We assessed studies against the following risk of bias criteria, in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* 5.1.0 (Higgins 2011): random sequence generation, allocation concealment, blinding of participants, blinding of clinical operators, blinding of periodontal outcome assessment, incomplete outcome data, selective outcome reporting, and other potential biases. We 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 being provided in one arm and not the other. We assessed each domain as being at low, high, or unclear risk of bias, with 'unclear' indicating either lack of information or uncertainty over the potential for bias.

Measures of treatment effect

For continuous outcomes (e.g. HbA1c, clinical outcomes) where studies used the same scale, we used the mean values and standard deviations (SDs) reported in the studies in order to express the estimate of effect as mean difference (MD) with 95% confidence interval (CI). When different scales were used, we expressed the treatment effect as standardised mean difference (SMD) with 95% CI. If there had been any dichotomous outcomes, we would have expressed the estimate of effect as a risk ratio (RR) with 95% CI.

Unit of analysis issues

The unit of analysis was the participant. Where multi-arm studies were included, we ensured participants were not double counted in meta-analyses.

Dealing with missing data

We attempted to contact trial authors to retrieve missing data when they were not available from the trial report, or to clarify areas where data or trial design and conduct were unclear. Where standard deviations were missing, we obtained these from a study's confidence intervals, P values or t values where available.

Assessment of heterogeneity

We assessed statistical heterogeneity by calculation of the Q statistic with P value set at $P < 0.10$. This was quantified by the calculation of the I^2 statistic for heterogeneity. We judged values above 75% to represent high heterogeneity and values from 50% to 74% as moderate, based on guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

For the primary outcome, where there were sufficient studies (more than 10 per comparison), we assessed publication bias by generating funnel plots, which may indicate potential presence of

reporting biases if asymmetric, and via the Begg and Mazumdar adjusted rank correlation test (Begg 1994), and the Egger et al regression asymmetry test (Egger 1997).

Data synthesis

We conducted meta-analysis where studies were judged to be sufficiently similar. We used random-effects meta-analyses to combine quantitative data where there were at least four studies. We used the analysis method chosen by the trial authors, which was generally an intention-to-treat approach. All the data analysed were continuous. We expressed pooled outcomes as mean differences with their associated 95% confidence intervals. Where studies had more than one arm and provided data for two or more intervention groups, but only one control group, we divided the number of control participants by the number of comparisons involving the control arm, in order to avoid double-counting participants. We also did this where studies had more than one control group for the same intervention group, and adjusted the numbers in the intervention group in the same way.

Subgroup analysis and investigation of heterogeneity

For the primary outcome, where appropriate and possible, we used subgroup analyses to explore, quantify, and control for sources of heterogeneity between studies for the following..

- Intervention and control type - subgingival instrumentation versus usual care/no intervention, subgingival instrumentation plus systemic or locally delivered antimicrobial versus usual care, subgingival instrumentation plus antimicrobial mouthrinse (chlorhexidine) versus usual care/no intervention. (We did not anticipate finding any studies solely evaluating surgical interventions.)
- Type 1 versus type 2 diabetes mellitus.
- Diabetic control (poor (above 8.5% HbA1c) versus fair (7.5% to 8.4%) versus good (up to 7.5%)).
- Treatment setting: primary care (general practice settings), community care (public dental services), or secondary care (specialist-led care in a hospital setting).
- Inclusion of a maintenance regimen following the initial intervention treatment versus none (for studies lasting longer than 3 months).

Sensitivity analysis

For the primary outcome, we performed sensitivity analyses (where there were sufficient studies for each outcome) by excluding studies at high and unclear risk of bias (disregarding the domains for blinding of participants, clinical operators, and periodontal outcome assessors).

Summary of findings and assessment of the certainty of the evidence

We developed summary of findings tables for the main comparison and the outcomes glycaemic control measured by HbA1c (primary outcome) and adverse effects, using GRADEpro software (GRADEpro GDT). We assessed the certainty of the body of evidence with reference to the overall risk of bias of the included studies, directness of the evidence, consistency of the results, precision of the estimates, and risk of publication bias. The certainty of the body of evidence for each of the outcomes was categorised as high, moderate, low, or very low (GRADEpro GDT).

Incorporating economic evidence

This review includes a brief economic commentary (BEC), which follows the methodology described in Chapter 20 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). The BEC summarises the availability and principal findings of single study (e.g. trials or cohort studies) and model-based (e.g. decision tree or Markov) full economic evaluations. Full economic evaluations are defined as comparative assessments of costs, or costs and outcomes, within a cost-minimisation, cost-effectiveness, cost-utility, or cost-benefit analysis framework. We included studies that compared periodontal treatments versus none, or different types of periodontal treatments for adults with type 1 or type 2 diabetes.

One review author (Dwayne Boyers (DB)), who is a health economist, devised a literature search strategy to identify full economic evaluations for the BEC and conducted searches using NHS EED Ovid (NHS Economic Evaluation Database) up until March 2015, MEDLINE Ovid (from 2000 to 2 March 2022), and Embase Ovid (from 2000 to 2 March 2022). The Scottish Intercollegiate Guideline Network (SIGN) filter for identifying economic studies was used (SIGN 2022). The search strategies for the BEC are reported in Appendix 2.

Review author DB selected the studies and extracted the following data from relevant articles: analytical framework (single study or model-based economic evaluations), type of economic valuation (cost-minimisation, cost-effectiveness, cost-utility, cost-benefit analysis), analytical perspectives (healthcare payer, patient, societal), time horizon (i.e. length of time over which outcomes and costs are measured), setting, main cost items (including currency and price year), principal findings of the analyses, and any notable uncertainties explored.

The BEC focuses on the extent to which the principal findings of the identified full economic evaluations indicate that periodontal treatment among adults with diabetes may be judged favourably (or unfavourably) from an economic perspective. We did not critically appraise the studies.

RESULTS

Description of studies

Results of the search

Our updated search identified 3109 records, which reduced to 2062 after removal of duplicates. We rejected irrelevant articles and set aside those eligible for inclusion in our review of head-to-head trials. We found six studies (eight records) that we thought should be formally excluded with reasons. We found one paper relating to an already included study (Engebretson 2013). This left 19 trials (23 records) suitable for inclusion in the review from our new searches.

The previous version of the review included 35 trials, 19 of these assessed a head-to-head comparison so were set aside for the sister review, and 16 of them (27 records) were brought forward into this review as they assessed a relevant periodontal treatment versus no/delayed treatment or usual care (Calbacho 2004; Chen 2012; Engebretson 2013; Gay 2014; Jones 2007; Katagiri 2009; Kiran 2005; Koromantzos 2011; Kothiwale 2013; Li 2011; Moeintaghavi 2012; Raman 2014; Singh 2008; Sun 2011; Yun 2007; Zhang 2013). We refined the excluded studies list from the previous version,

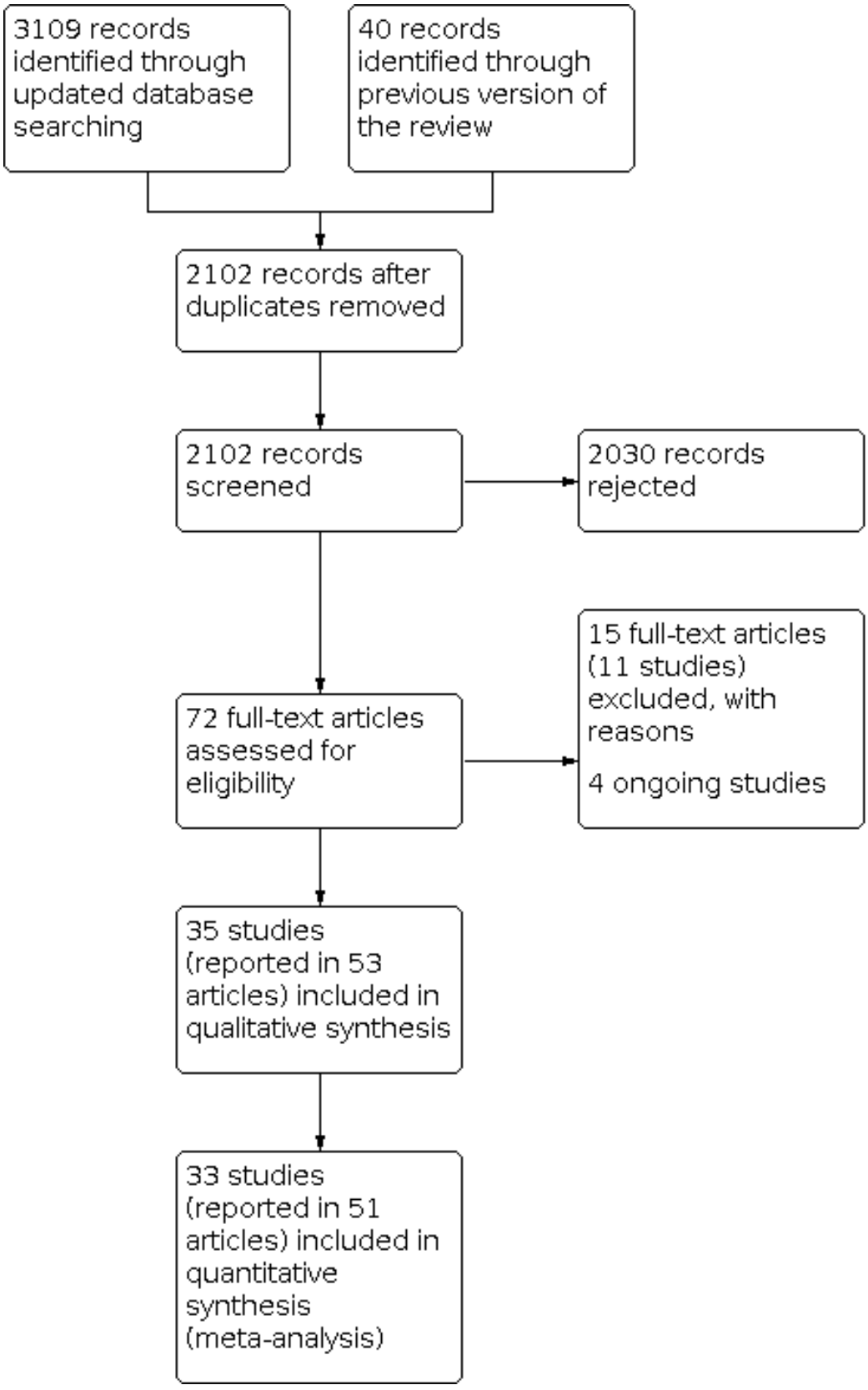
deleting those that were clearly ineligible or related to head-to-head trials, and we checked the studies awaiting classification and ongoing studies. The result of this process was to bring forward into this version of the review, five excluded studies (seven records) (Albrecht 1988; Botero 2013; Chee 2006; Khader 2010; NCT01255254) and four ongoing studies (ACTRN12605000260628; NCT01291875; NCT01901926; U1111-1124-3635). A further two ongoing studies related to two of the new included studies so were added as additional references (D'Aiuto 2018; Vergnes 2018).

See Additional Table 1 for details of study selection for earlier versions of the review.

Therefore, for this version of the review, we have 35 included studies (53 records) (see Characteristics of included studies), 11 excluded studies (15 records) (see Characteristics of excluded studies), and 4 ongoing studies (see Characteristics of ongoing studies).

We generated a PRISMA diagram to illustrate the study selection process: Figure 1.

Figure 1. Study selection process.



Included studies

We identified 35 studies that compared periodontal treatment with no treatment, placebo, or usual care (Artese 2015; Bukleta 2018; Calbacho 2004; Chen 2012; D'Aiuto 2018; Das 2019; El-Makaky 2020; Engebretson 2013; Felipe 2015; Gay 2014; Jones 2007; Kapellas 2017; Katagiri 2009; Kaur 2015; Kiran 2005; Koromantzos 2011; Kothiwale 2013; Lee 2020; Li 2011; Mauri-Obradors 2018; Mizuno 2017; Moeintaghavi 2012; Qureshi 2021; Raman 2014; Rapone 2021; Rodrigues 2015; Singh 2008; Sun 2011; Telgi 2013; Tsobgny-Tsague 2018; Vergnes 2018; Wang S 2017; Wang Y 2017; Yun 2007; Zhang 2013). The studies involved 3249 randomised participants in total.

Characteristics of studies

Design

To be included in this review, all studies had to be randomised controlled trials (RCTs). The included studies were all parallel design. Most studies compared two groups, with six studies comparing three groups (Chen 2012; Das 2019; Li 2011; Qureshi 2021; Singh 2008; Telgi 2013), and one comparing four, though two were not eligible for this review (Bukleta 2018).

Location

The included studies were conducted in the following countries:

- China: Chen 2012; Li 2011; Sun 2011; Yun 2007; Wang S 2017; Zhang 2013, and Hong Kong (Wang Y 2017);
- India: Das 2019; Kaur 2015; Kothiwale 2013; Singh 2008; Telgi 2013;
- Brazil: Artese 2015; Felipe 2015; Rodrigues 2015;
- USA: Engebretson 2013; Gay 2014; Jones 2007;
- Japan: Katagiri 2009; Mizuno 2017;
- Albania: Rapone 2021;
- Australia: Kapellas 2017;
- Cameroon: Tsobgny-Tsague 2018;
- Chile: Calbacho 2004;
- Egypt: El-Makaky 2020;
- France: Vergnes 2018;
- Greece: Koromantzos 2011;
- Iran: Moeintaghavi 2012;
- Korea: Lee 2020;
- Kosovo: Bukleta 2018;
- Malaysia: Raman 2014;
- Pakistan: Qureshi 2021;
- Turkey: Kiran 2005;
- Spain: Mauri-Obradors 2018;
- UK: D'Aiuto 2018.

Setting

Most studies were conducted in a hospital setting (secondary care). Two were conducted in a primary care setting (Calbacho 2004; Jones 2007) and three in a community setting (Engebretson 2013; Lee 2020; Li 2011). Four studies did not report the type of setting (Artese 2015; Chen 2012; Kapellas 2017; Rapone 2021).

Most studies were conducted from a single centre; nine were multicentred (Das 2019 (2 centres); Engebretson 2013 (5); Jones 2007 (4); Kapellas 2017 (4); Katagiri 2009 (5); Li 2011 (6); Mauri-Obradors 2018 (3); Raman 2014 (2); Vergnes 2018 (2)); and one did not report how many centres were involved (Calbacho 2004).

Funding

See Characteristics of included studies for details of funding sources for each study, as well as any conflicts of interest.

Follow-up

Longest follow-up varied in the studies, ranging from 3 to 12 months.

- Seventeen studies followed up their participants for 3 months (Bukleta 2018; Das 2019; El-Makaky 2020; Felipe 2015; Kapellas 2017; Kiran 2005; Kothiwale 2013; Lee 2020; Moeintaghavi 2012; Raman 2014; Rodrigues 2015; Singh 2008; Sun 2011; Telgi 2013; Tsobgny-Tsague 2018; Vergnes 2018; Wang S 2017) and four trials followed up for 4 months (Calbacho 2004; Gay 2014; Jones 2007; Yun 2007). We did not consider there to be a clinically significant difference between 3 and 4 months, and so we pooled data from these time points in our meta-analyses ('3-4 months').
- Thirteen studies followed up their participants for 6 months (Artese 2015; Chen 2012; Engebretson 2013; Katagiri 2009; Kaur 2015; Koromantzos 2011; Li 2011; Mauri-Obradors 2018; Mizuno 2017; Qureshi 2021; Rapone 2021; Wang Y 2017; Zhang 2013).
- One study followed up participants for 12 months (D'Aiuto 2018).

Characteristics of participants

The largest study randomised 514 participants (Engebretson 2013), and the second largest, 264 (D'Aiuto 2018). The sample size in the other studies ranged from 18 to 193 participants.

Included trials spanned a broad range of ages from 18 to 80 years. Some studies did not report an age range for inclusion.

All but one of the studies included participants with type 2 diabetes; one study assumed participants to all be T2DM without confirmed diagnosis (Jones 2007). One 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 (glycated haemoglobin) of participants at baseline, with consequent variation in the potential for improvement in glycaemic control as a result of the intervention. We categorised diabetic control to be poor (above 8.5% HbA1c), fair (7.5% to 8.4%), or good (up to 7.5%). The information studies usually provided about participant HbA1c at baseline was the mean and standard deviation per group. Based on this, most studies were mixed and involved participants with good, fair, or poor metabolic control. Further details are provided in the Characteristics of included studies section.

The use of antidiabetic therapy and whether this was changed during the study conduct period varied across the trials (see Characteristics of included studies for further details). The severity of periodontitis also varied across studies. See Additional Table 2 for more details about the diagnoses of periodontitis and diabetes.

Characteristics of interventions and comparisons

We formed three main subgroups for interventions:

- subgingival instrumentation versus no treatment/usual care;

- subgingival instrumentation plus systemic/locally delivered antimicrobials versus no treatment/usual care; and
- subgingival instrumentation plus antimicrobial mouthrinse (chlorhexidine) versus no treatment/usual care.

A more detailed description of the specific interventions included in each comparison is presented in the Characteristics of included studies tables.

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

Surgical treatment was included in a subset of patients only in one study (D'Aiuto 2018).

For studies that lasted 6 months or longer, most provided maintenance treatment if required at 3 and 6 months to participants in the intervention group(s): Chen 2012 (intervention group A); D'Aiuto 2018; Engebretson 2013; Katagiri 2009; Kaur 2015; Koromantzos 2011; Mauri-Obradors 2018; Mizuno 2017; Katagiri 2009. Wang Y 2017 and Zhang 2013 did not provide maintenance treatment, and details were unclear in Li 2011 and Qureshi 2021.

A number of studies also included extraction of teeth deemed 'hopeless' as part of the intervention. We did not evaluate this intervention as it is not strictly periodontal treatment, although this may contribute to reductions in HbA1c by reducing inflammation associated with 'hopeless' teeth.

Characteristics of outcomes

Primary outcome

To be included in this review, studies had to measure HbA1c. Two included studies did not present results for HbA1c in a way that allowed them to be used in our meta-analysis of mean percentage (Artese 2015 (graph); Rapone 2021 (statistical test results only)).

HbA1c was measured at 3 to 4 months in 30 studies (Bukleta 2018; Calbacho 2004; Chen 2012; Das 2019; El-Makaky 2020; Engebretson 2013; Felipe 2015; Gay 2014; Jones 2007; Kapellas 2017; Katagiri 2009; Kaur 2015; Kiran 2005; Koromantzos 2011; Kothiwale 2013; Lee 2020; Li 2011; Mizuno 2017; Moeintaghavi 2012; Qureshi 2021; Raman 2014; Rodrigues 2015; Singh 2008; Sun 2011; Telgi 2013; Tsobgny-Tsague 2018; Vergnes 2018; Yun 2007; Wang S 2017; Zhang 2013); nine of which also reported at 6 months (Chen 2012; Engebretson 2013; Katagiri 2009; Kaur 2015; Koromantzos 2011; Li 2011; Mizuno 2017; Qureshi 2021; Zhang 2013). One study reported at 6 months only (Wang Y 2017), and one study reported at 6 and 12 months (D'Aiuto 2018).

Secondary outcomes

- Clinical attachment level (CAL): 18 studies reported at 3 to 4 months; five studies reported at 6 months. Measured as change from baseline in mm.
- Probing pocket depth (PPD): 21 studies reported at 3 to 4 months; eight studies reported at 6 months; one study reported at 12 months. Measured in mm.
- Bleeding on probing (BOP): 14 studies reported at 3 to 4 months; seven studies reported at 6 months. Measured as percentage of sites with bleeding.
- Plaque index (PI): 18 studies reported at 3 to 4 months; eight studies reported at 6 months; one study reported at 12 months. Different plaque indices reported: percentage of sites with plaque, Silness and Loe (see footnotes in forest plots). Standardised mean difference was used to pool data.
- Gingival index (GI): 12 studies reported at 3 to 4 months; six studies reported at 6 months; one study reported at 12 months. Different gingival indices reported: Loe and Silness, sulcus bleeding index (see footnotes in forest plots). Standardised mean difference was used to pool data.
- Adverse effects: seven studies reported some adverse events (D'Aiuto 2018; Jones 2007; Koromantzos 2011; Mauri-Obradors 2018; Qureshi 2021; Tsobgny-Tsague 2018; Vergnes 2018) and six studies reported that there were no adverse effects (Chen 2012; Das 2019; El-Makaky 2020; Engebretson 2013; Mizuno 2017; Singh 2008). The remainder (22) did not report whether there were any adverse events or not.
- Three included studies reported data relating to quality of life (D'Aiuto 2018; Mizuno 2017; Vergnes 2018).
- The studies did not report on cost implications or diabetic complications.

Excluded studies

After examination of full-text papers, we excluded 11 studies as they failed to meet our inclusion criteria. The reasons for exclusion are detailed in the Characteristics of excluded studies tables:

- observational study (ChiCTR2000030393);
- no mention of randomisation (Elsadek 2020; Mammen 2017);
- quasi-randomised (Goel 2017; Peña Sisto 2018);
- poorly reported and inclusion unclear despite attempts to contact authors (Botero 2013; Chee 2006);
- HbA1c not reported (Albrecht 1988);
- inappropriate intervention (full-mouth tooth extraction) (Khader 2010);
- trial abandoned (NCT01255254);
- cluster-randomised trial (two health centres, one randomised to each intervention) (Phetnin 2020).

Risk of bias in included studies

Two review authors independently assessed risk of bias for each included study, and a risk of bias table for each was completed (Characteristics of included studies). Results are presented graphically by study (Figure 2). All studies were at high risk of bias for blinding of participants and clinical operators as this cannot be avoided in these type of trials. We did not consider blinding of outcome assessment for our primary outcome as this was objective. Therefore, excluding blinding, our assessment of overall risk of bias for our primary outcome was 14 studies at high risk of bias (Artese 2015; Bukleta 2018; Calbacho 2004; Felipe 2015; Gay 2014; Jones 2007; Kapellas 2017; Katagiri 2009; Kothiwale 2013; Mauri-Obradors 2018; Qureshi 2021; Raman 2014; Sun 2011; Zhang 2013), 2 at low risk (Kiran 2005; Wang S 2017), and 19 unclear.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

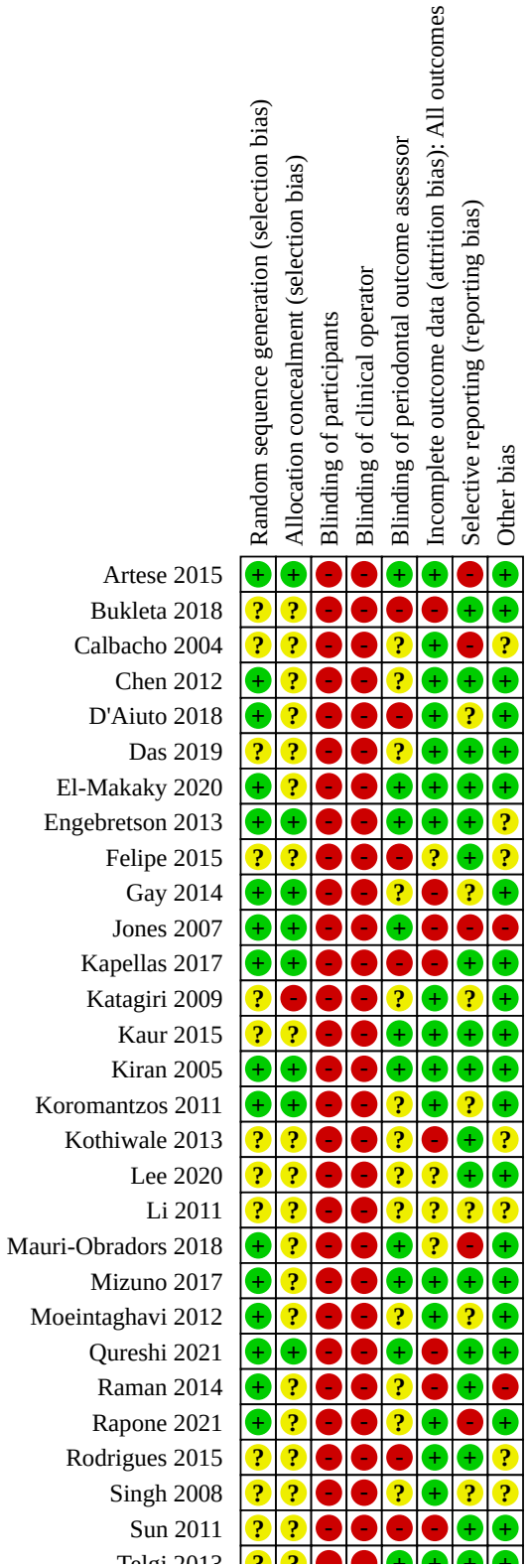
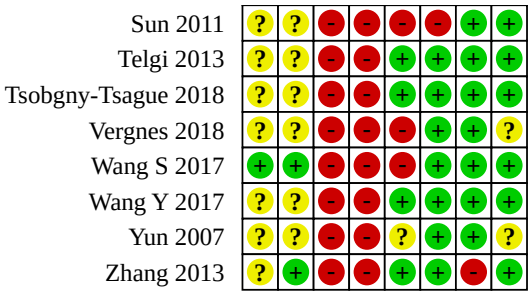


Figure 2. (Continued)



Allocation

We judged studies for selection bias based on the adequacy of random sequence generation and allocation concealment (to prevent selective enrolment).

Nine studies reported adequate random sequence generation and allocation concealment and so were judged to be at low risk of selection bias (Artese 2015; Engebretson 2013; Gay 2014; Jones 2007; Kapellas 2017; Kiran 2005; Koromantzos 2011; Qureshi 2021; Wang S 2017).

One study was judged to be at high risk of selection bias due to inadequate allocation concealment (Katagiri 2009).

Twenty-five studies were judged to be at unclear risk of selection bias, mainly due to lack of information about allocation concealment.

Blinding

Performance bias

For the primary outcome, HbA1c, all studies were at high risk of bias as it is not possible to blind participants or clinical operators.

Detection bias

We did not assess the studies for detection bias in HbA1c as HbA1c tests were carried out remotely, therefore all studies were considered to be at low risk.

In terms of blinded outcome assessment for periodontal outcomes, we judged 13 studies as at low risk of bias for blinded outcome assessment (Artese 2015; El-Makaky 2020; Engebretson 2013; Jones 2007; Kaur 2015; Kiran 2005; Mauri-Obradors 2018; Mizuno 2017; Qureshi 2021; Telgi 2013; Tsobgny-Tsague 2018; Wang Y 2017; Zhang 2013), 14 studies as unclear, and eight at high risk of bias (Bukleta 2018; D'Aiuto 2018; Felipe 2015; Kapellas 2017; Rodrigues 2015; Sun 2011; Vergnes 2018; Wang S 2017).

Incomplete outcome data

We judged 23 studies at low risk of bias, with many studies reporting no loss of follow-up. Eight studies were assessed as at high risk of attrition bias (Bukleta 2018; Gay 2014; Jones 2007; Kapellas 2017; Kothiwale 2013; Qureshi 2021; Raman 2014; Sun 2011), and four were unclear (Felipe 2015; Lee 2020; Li 2011; Mauri-Obradors 2018).

Selective reporting

Twenty-two studies were judged to be at low risk of bias, six studies at high (Artese 2015; Calbacho 2004; Jones 2007; Mauri-Obradors 2018; Rapone 2021; Zhang 2013), and seven studies as unclear (D'Aiuto 2018; Gay 2014; Katagiri 2009; Koromantzos 2011; Li 2011; Moeintaghavi 2012; Singh 2008).

Other potential sources of bias

Twenty-four studies were judged to be at low risk of bias, two studies at high (Jones 2007; Raman 2014), and nine studies at unclear (Calbacho 2004; Engebretson 2013; Felipe 2015; Kothiwale 2013; Li 2011; Rodrigues 2015; Singh 2008; Vergnes 2018; Yun 2007).

Effects of interventions

See: **Summary of findings 1** Periodontal treatment compared to no treatment/usual care for glycaemic control in people with diabetes mellitus

Periodontal treatment versus no active intervention/usual care

Primary outcome

The summary for this primary outcome is given in Summary of findings 1. Two studies that measured HbA1c could not be included in meta-analysis because of the way they reported results: Artese 2015 (6 months) and Rapone 2021 (3 and 6 months).

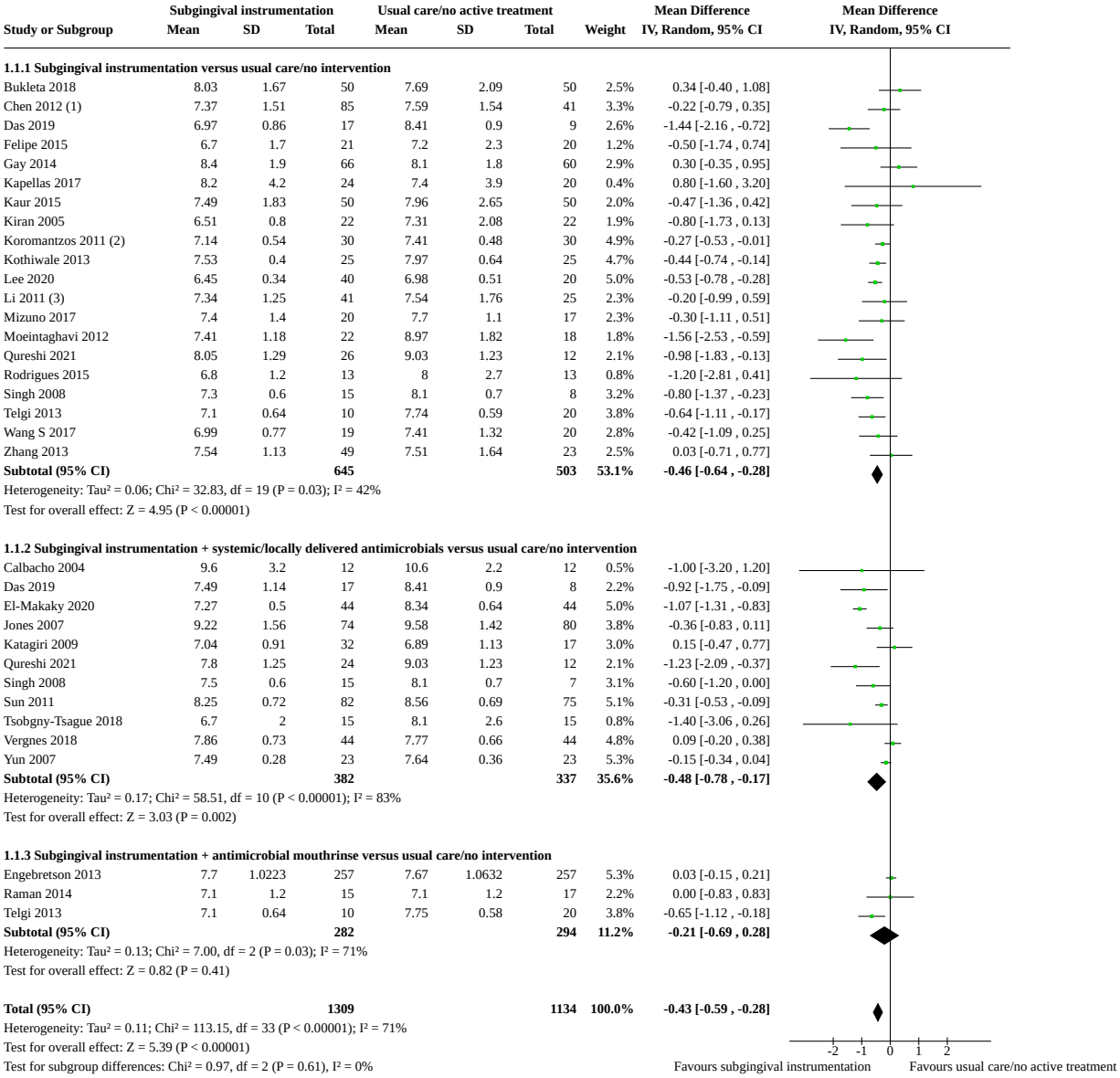
HbA1c: 3 to 4 months

Thirty studies (2443 analysed participants) compared periodontal treatment against no active intervention/usual care at 3 or 4 months. Eighteen studies were assessed as at high risk of bias (excluding the three domains relating to blinding), 11 studies were assessed as at unclear risk of bias, and one study (Kiran 2005) was assessed as at low risk of bias. Overall, there was a benefit for periodontal treatment with a mean absolute reduction in HbA1c of 0.43% (4.7 millimoles per mole (mmol/mol); 95% confidence interval (CI) -0.59% to -0.28%; -6.4 mmol/mol to -3.0 mmol/mol; effect $P < 0.001$). There was a moderate amount of heterogeneity ($P < 0.001$; $I^2 = 71\%$) (Analysis 1.1).

Three subgroups were formed to explore any potential impact of adjuncts to periodontal treatment: subgingival instrumentation (20 studies), subgingival instrumentation plus antimicrobials (11 studies), and subgingival instrumentation and antimicrobial mouthrinse (three studies). Four studies contributed data to more than one subgroup (Das 2019; Qureshi 2021; Singh 2008; Telgi

2013). There was no statistically significant difference between the subgroups (P = 0.61) (Figure 3).

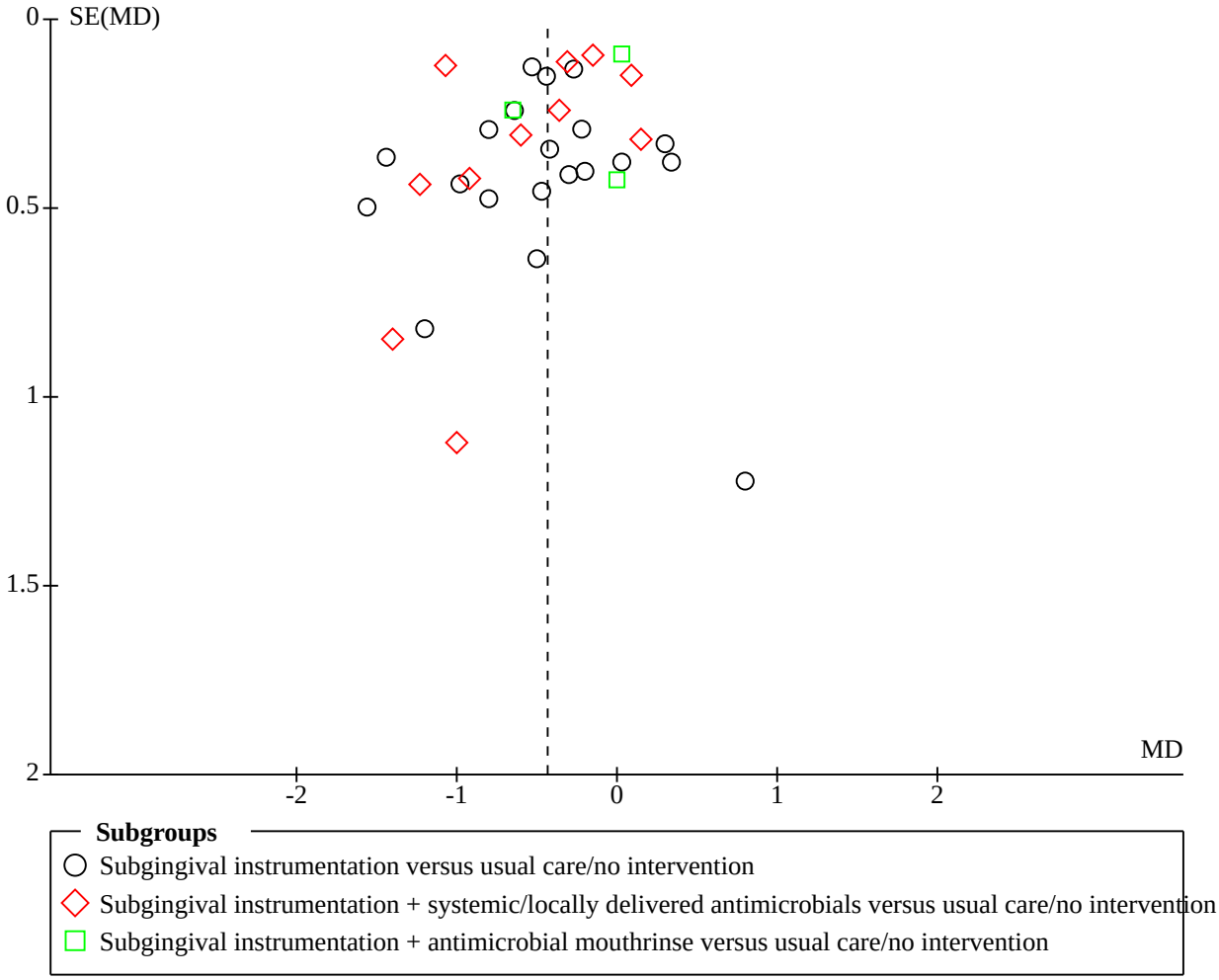
Figure 3. Forest plot of comparison: 1 Periodontal treatment versus no active intervention/usual care, outcome: 1.1 HbA1c at 3-4 months.



Footnotes
(1) SGI + additional mechanical therapy
(2) SGI + OHI vs mechanical therapy (supragingival cleaning) + OHI
(3) Periodontal treatment described as "mechanical therapy"

A funnel plot of the 30 included studies (Figure 4: reflecting the four studies contributing to two subgroups) failed to indicate any relationship between mean percentage reduction in HbA1c and precision (related to sample size). The Egger formal test for asymmetry intercept was not statistically significant: -0.58 (95% CI -1.89 to 0.72; P = 0.37) (Egger 1997).

Figure 4. Funnel plot of comparison: 1 Periodontal therapy versus no active intervention/usual care, outcome: 1.1 HbA1c at 3-4 months.

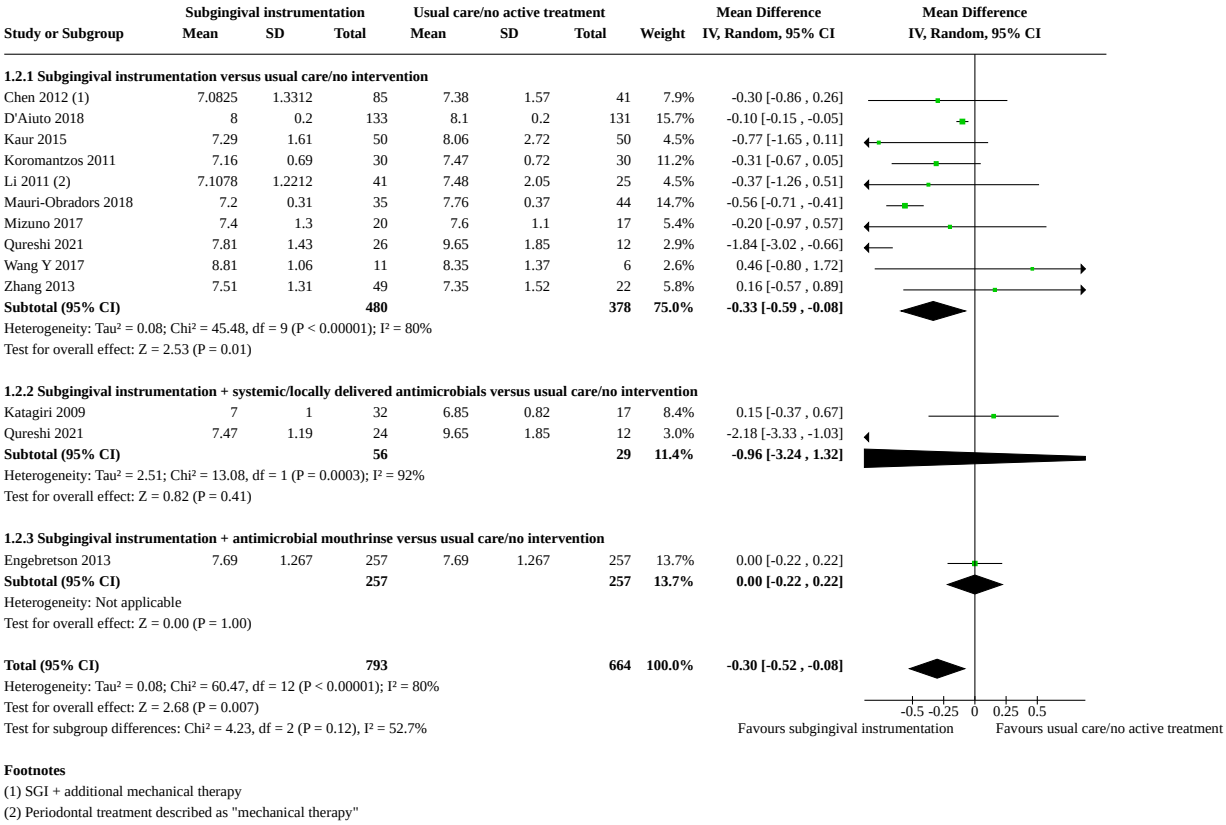


HbA1c: 6 months

Twelve studies (1457 participants) compared periodontal treatment against no active intervention/usual care at 6 months. Six studies were assessed as at high risk of bias (excluding the three domains relating to blinding) and three studies were assessed as at unclear risk of bias. Overall, there was benefit for periodontal treatment with mean absolute reduction in HbA1c of 0.30% (3.3 mmol/mol; 95% CI -0.52% to -0.08%; -5.7 mmol/mol to -0.9 mmol/mol; effect P = 0.007). There was evidence of substantial heterogeneity (P < 0.0001; I^2 = 80%).

The same three subgroups as above were formed for studies: subgingival instrumentation (SGI) (10 studies), SGI plus antimicrobials (two studies), and SGI and antimicrobial mouthrinse (one study), all compared against usual care or no intervention. One study was included in two of the subgroups (Qureshi 2021). It was inappropriate to conduct a subgroup analysis with a single study in one of the subgroups (Analysis 1.2; Figure 5).

Figure 5. Forest plot of comparison: 1 Periodontal treatment versus no active intervention/usual care, outcome: 1.2 HbA1c at 6 months.

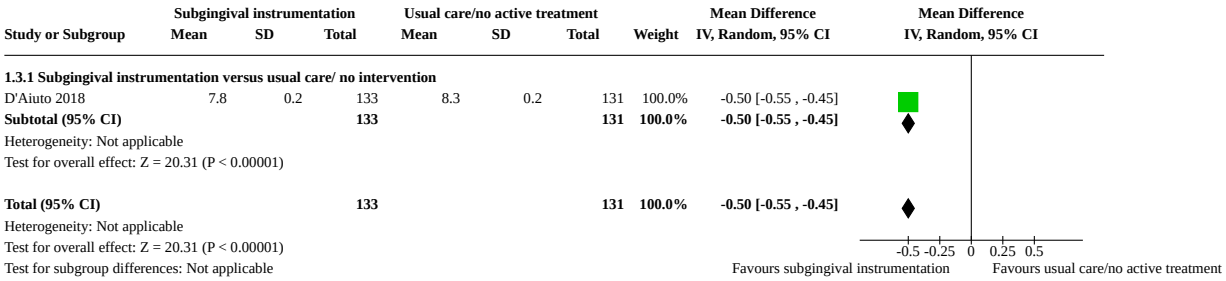


Footnotes
(1) SGI + additional mechanical therapy
(2) Periodontal treatment described as "mechanical therapy"

HbA1c: 12 months

One study (D'Aiuto 2018), assessed at unclear risk of bias, compared subgingival instrumentation against no active intervention/usual care and provided data for the primary outcome at 12 months. The study showed a benefit for periodontal treatment with a mean absolute reduction in HbA1c of 0.50% (5.4 mmol/mol; 95% CI -0.55% to -0.45%; -6.0 mmol/mol to -4.9 mmol/mol; effect P < 0.001; Figure 6).

Figure 6. Forest plot of comparison: 1 Periodontal treatment versus no active intervention/usual care, outcome: 1.3 HbA1c at 12 months.



Investigating heterogeneity and sensitivity analyses for HbA1c

As reported in the section above, the subgroup analyses shown in the forest plots for the three different periodontal treatments showed no evidence of differences between the treatments at any time point.

We were unable to investigate differences due to whether participants were diagnosed with type 1 or type 2 diabetes as no studies were conducted solely with participants with type 1 diabetes and only one study included participants with both type 1 and type 2 diabetes (Vergnes 2018). The HbA1c effect size for this study was 0.09% (1 mmol/mol; 95% CI -0.20% to 0.38%; -2.2 mmol/mol to 4.1 mmol/mol) at 3 to 4 months, which is lower than the overall estimate. However, there is insufficient evidence to determine whether there is a difference between this study and the others.

For studies measuring outcomes at 3 to 4 months, 23 studies were conducted in a hospital setting (secondary care), two were conducted in a primary care setting (Calbacho 2004; Jones 2007), and three in a community setting (Engebretson 2013; Lee 2020; Li 2011). For studies measuring results at 6 months, nine studies were conducted in secondary care and two in a community setting. A subgroup analysis for setting was conducted at 3 to 4 months and 6 months and the results are summarised in Additional Table 3. There was no evidence of a difference between the subgroups at either 3 to 4 months or 6 months (P = 0.59; P = 0.06), so differences in setting did not explain the heterogeneity.

The classification of the studies with respect to the diabetes control of the patients is presented in the Included studies, 'Characteristics of participants' section. There was considerable overlap with this, which meant we were unable to investigate the heterogeneity through subgroup analysis based on how well diabetes was controlled.

For studies providing data at 6 months, maintenance was provided following the initial periodontal treatment in eight studies, with three studies not providing maintenance. One study had two arms, with one included in each subgroup (Chen 2012). The results of the subgroup analysis are provided in Additional Table 4 and there is no evidence of a difference between the subgroups (P = 0.58), and differences in maintenance did not explain the heterogeneity.

A sensitivity analysis was conducted for the two studies that were assessed as at low risk of bias (excluding the domains of participant, clinical operator and outcome assessor blinding) at 3 to 4 months (Kiran 2005; Wang S 2017), resulting in the effect estimate -0.55% (-6.0 mmol/mol; 95% -1.10% to -0.00%; -12.0 mmol/mol to 0.0 mmol/mol), which is similar to the overall effect size. No studies were assessed as at low risk of bias at 6 months.

Secondary outcomes

Periodontal indices

The forest plots for the periodontal outcomes at 3 to 4, 6, and 12 months are presented in Analysis 1.4 to Analysis 1.16. Details of these indices are given in the Included studies section.

Additional Table 5 documents the clinical periodontal secondary outcomes for the studies included in this comparison at both 3 to 4, and 6 months. There was evidence of a difference in favour of periodontal treatment for all periodontal indices (clinical attachment level (CAL), probing pocket depth (PPD), bleeding on probing (BOP), plaque index (PI), and gingival index (GI)) at both 3 to 4, and 6 months follow-up (P < 0.001). There was substantial heterogeneity between the studies for all the indices at both time points. There was evidence of benefit of periodontal treatment for three periodontal outcomes (PPD, PI, and GI) at 12 months from one study.

Adverse effects

Twenty-two studies did not report whether or not their participants experienced any adverse effects from their allocated treatment (Artese 2015; Bukleta 2018; Calbacho 2004; Felipe 2015; Gay 2014; Kapellas 2017; Katagiri 2009; Kaur 2015; Kiran 2005; Kothiwale 2013; Lee 2020; Li 2011; Moeintaghavi 2012; Raman 2014; Rapone 2021; Rodrigues 2015; Sun 2011; Telgi 2013; Wang S 2017; Wang Y 2017; Yun 2007; Zhang 2013). Where loss to follow-up was reported, no detailed reasons for most participants failing to complete were provided.

Three studies suggested their participants experienced side effects but no clear serious adverse effects or they were unable to monitor for side effects/adverse events (Koromantzos 2011; Qureshi 2021; Tsobgny-Tsague 2018). Koromantzos 2011 found no specific adverse events but noted five participants required a change in insulin dosage. Qureshi 2021 had a large number of participants lost to follow-up, but no specific side effects or adverse events were monitored and none reported. The authors made a “general observation... that the participants were unable to make up or follow up visits in fasting state which was required for their biochemical testing.” Tsobgny-Tsague 2018 reported a minor side effect of one case of tongue irrigation following chlorhexidine mouthrinse in the treatment group.

Six 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). Although Engebretson 2013 reported that there were no serious study-related adverse effects, 2 weeks after treatment, they reported that the intervention group experienced more soreness, tenderness, pain, and thermal sensitivity than the control group. These symptoms are common sequelae of subgingival instrumentation.

Four studies gave details on adverse effects observed (D'Aiuto 2018; Jones 2007; Mauri-Obradors 2018; Vergnes 2018).

D'Aiuto 2018 gave a breakdown of adverse events according to how serious they were. Eleven (8%) of the 133 participants in the intensive periodontal therapy treatment group experienced a serious adverse event; three (3%) had two or more serious adverse events. In addition, one participant (1%) had a serious adverse event causing death. In the control group (n = 131), 11 (8%) had a serious adverse event and two (2%) had two or more serious adverse events. In addition, two (2%) experienced a serious adverse event causing death. Serious adverse events in the intensive periodontal therapy group included “toe gangrene, pneumonia, spine surgery, fall, car accident, stroke, gastric surgery, coronary angioplasty, hypoglycaemia, confusion or disorientation, lung resection, kidney stones, and prostate hypertrophy; serious adverse events reported in the control periodontal therapy group include chest pain (heartburn), hypertensive crisis, femoral fracture, pneumonia, alcoholic liver disease, acute episode of irritable bowel syndrome, spine surgery, and hip replacement. The serious adverse event resulting in death reported in the intensive periodontal therapy group was acute kidney failure; the serious adverse events resulting in death reported in the control periodontal therapy group were myocardial infarction, heart failure, and stroke.” These events are unlikely to be related to the study intervention and more likely reflect the underlying comorbidities in the study population.

Furthermore, less serious adverse events were documented by frequency and category (see Additional Table 6).

Jones 2007 found “the most commonly reported symptoms among veterans taking doxycycline were gastrointestinal: diarrhea (7.1%),

abdominal pain (3.6%), and nausea (2.9%). Among subjects using chlorhexidine, the most common symptoms were changes in taste (15.0%), tooth staining (13.6%), and sore mouth or tongue tip irritation (5.0% each). Swelling of the face, lips, and throat and shortness of breath were also reported."

Mauri-Obradors 2018 noted that several participants dropped out for medical reasons. Four dropouts occurred in the treatment group, one with ictus and one angina. There were seven dropouts in the control arm, one with ictus, one psychiatric disease, one kidney failure, and one for trauma. Again, these events are likely reflective of comorbid conditions within the population, rather than being related to periodontal treatment.

Vergnes 2018 noted that "during the 3-month follow-up period, 23 subjects in the control group and 22 subjects in the treatment group reported having a health problem that might affect the course of the clinical trial (P > 0.99). 15 and 18 control and treatment subjects, respectively, experienced oral disorders (P = 0.37). The treatment group experienced more dental hypersensitivity (P = 0.03) but with a tendency towards less diffuse pain (P = 0)."

Adverse effects observed in head-to-head trials will be described in the sister review to this one, which will focus on the head-to-head comparisons of one periodontal treatment versus another.

Quality of life

Only three studies measured quality of life (QoL) as an outcome (D'Aiuto 2018; Mizuno 2017; Vergnes 2018). The available evidence is sparse and mixed, but there is some limited evidence of a possible benefit from periodontal treatment in terms of QoL as it relates to some aspects of living with diabetes and periodontitis.

D'Aiuto 2018, which randomised 264 participants with 'fair' diabetes control and moderate-to-severe periodontitis, measured QoL at 12 months using the Audit of Diabetes-Dependent Quality of Life questionnaire. By 12 months, 20 participants were lost to follow-up (12 intervention, 8 control), but intention-to-treat (ITT) analysis was used. D'Aiuto 2018 found lower (better) scores in the intervention group: 0.83, 95% CI 0.29 to 1.38; P = 0.0034), which was mainly due to the changes in working life (difference 1.12, 95% CI 0.37 to 1.86; P = 0.0029), self-confidence (difference 0.48, 95% CI 0.17 to 1.22; P = 0.0413), and living conditions (difference 0.81, 95% CI 0.40 to 1.43; P = 0.0096) domains of the test.

Mizuno 2017 measured QoL using the Diabetes Therapy-Related QOL (DTR-QOL) questionnaire. DTR-QOL comprises four factors: 1) burden on social activities and daily activities, 2) anxiety and dissatisfaction with treatment, 3) hypoglycaemia, and 4) satisfaction with treatment. QoL was measured at 3 and 6 months from baseline. Participants in the study had type 2 diabetes mellitus, with 'fair' diabetes control, and 'chronic periodontitis'. This was a small study with 20 people randomised to each group, and only 14 in the intervention group and 17 in the control group remaining by final follow-up. The authors conducted both intention-to-treat (last observation carried forward) and per-protocol analyses. The authors reported that QoL significantly improved in the periodontal treatment group compared to the control group at 3 months. However, this was only seen in one factor of the questionnaire and at one time point - treatment satisfaction at 3 months (3.68, 95% CI 0.25 to 7.10; 37 participants, ITT analysis). For the overall DTR-QOL score, there was no evidence of a difference between groups at 3 months (2.56, 95% CI -30.73 to 35.86; 37 participants, ITT analysis) or 6 months (22.38, 95% CI -6.71 to 51.47; 37 participants, ITT analysis).

In the protocol for the Vergnes 2018 trial, QoL was to be measured at 3 months using the SF-36 (short form 36) questionnaire; however, in the study report, they had measured QoL using both SF-36 and an oral health-related quality of life (OHRQoL) assessment, the General Oral Health Assessment Index (GOHAI). Vergnes 2018 found the mean overall GOHAI score increased in the treatment group compared to the control group (adjusted mean difference (MD) 7.0, 95% CI 2.4 to 11.6; 79 participants), which was due to improvements in the 'psychological impacts' and 'pain and discomfort' domains. Similar results were obtained for ITT and per-protocol analyses. Most domains on the SF-36 did not show a difference between intervention and control groups, other than a greater improvement in the general health domain of the SF-36 for people with type 1 diabetes (adjusted MD 6.3, 95% CI 0.4 to 12.2; 58 participants). The study authors concluded that "there was no obvious evidence of an improvement in general QoL after periodontal treatment. However, there was significant improvement in oral health-related QoL."

Diabetic complications

The included studies did not report data on diabetic complications, although some provided information on medication changes during the study (see Characteristics of included studies for further details).

Cost implications

The included studies did not report data on cost implications. However, we produced a brief economic commentary to consider potential cost-effectiveness of periodontal intervention on diabetes management. This work was undertaken by a single author (Dwayne Boyers (DB)).

Brief economic commentary (BEC)

One review author (DB) looked for single-study and model-based economic evaluations of periodontal treatment compared to none, and comparisons of different periodontal treatments for people with diabetes to supplement the review. Using the BEC search strategy (Appendix 2), we identified four relevant full economic evaluations.

Two studies conducted retrospective analyses of medical and dental claims databases to establish the impact of periodontal treatment on healthcare costs for patients with diabetes (Nasseh 2017; Smits 2020). Given the longitudinal nature of the datasets and comparative interpretation (periodontal treatment versus none) of the included studies' analysis models, these studies have been interpreted as cost-minimisation analyses for the purposes of the BEC, as they provide useful insight into the potential cost implications of periodontal treatments for patients with diabetes. Smits 2020 conducted a retrospective analysis of medical and dental claims data from a Dutch health insurance company between 2012 and 2018. The study, which included claims from over 40,000 people with type II diabetes, found that average diabetes-related healthcare costs (2012 EUR) were EUR 12.03 (95% CI EUR 15.77 to EUR 8.29) lower per quarter of each year, for those receiving any periodontal treatment compared to those not receiving periodontal treatment. Nasseh 2017 conducted a similar study using an integrated dental, medical, and pharmacy commercial claims database in the USA. The study included 15,000 newly diagnosed type II diabetes patients with continuous

insurance coverage for 3 to 4 years following their initial diabetes claim. Using the authors' preferred analysis model, the study found that total healthcare costs (pharmacy, medical, and dental) were (costing year unclear, USD) USD 1799 lower (P < 0.01) for those who received any periodontal therapy compared to those who received none. Average cost savings were USD 408 (P < 0.05) when the analysis was restricted to diabetes-related healthcare costs alone, indicating the impact of periodontal treatment may extend more broadly beyond healthcare use for diabetes-related complications alone.

Neither of these retrospective claims analyses prove causality of the impact of periodontal treatment on costs, but they are indicative of the potential for reduced healthcare resource use and therefore cost savings over the medium term. It should also be noted that the studies do not include the longer-term effects of better periodontitis or diabetes control on healthcare resource use, or the impact of any health effects of the interventions in the longer term. While studies showing cost-savings are an important part of improving the efficiency of healthcare delivery, they alone do not provide evidence of cost-effectiveness of long-term treatment and maintenance, which is better explored in cost-effectiveness or cost-utility analyses.

The other two studies identified conducted decision analysis models reporting cost-utility (cost per quality adjusted life year (QALY)) analyses, over a life-time horizon (Choi 2020; Soloweij-Wedderburn 2017). Soloweij-Wedderburn 2017 evaluated the cost-utility, from a UK health and dental care payer perspective, of non-surgical periodontal treatment (scaling and root planing, followed by lifetime maintenance therapy and re-treatment as needed) compared with routine scale and polish as part of regular dental care. Lifetime costs and QALYs were considered in the model, but full details of the model structure and calculations were not provided. The model focused primarily on costs and outcomes for the diabetes care pathway, but also included assumptions about the impact of periodontal treatment on tooth loss. The model produced incremental cost-effectiveness ratios (ICERs), in 2004/2005 GBP, ranging from GBP 11,135 to GBP 35,023 per QALY gained for different age and baseline HbA1c values. Sensitivity analyses showed that the results were particularly sensitive to several highly uncertain model parameters, including the impact of periodontal treatment on HbA1c, compliance with treatment, and the proportion of compliant patients who respond to periodontal treatment. The study showed that periodontal treatment may be cost-effective for type 2 diabetes patients in the UK, but noted that several areas of uncertainty remained. Choi 2020 developed a comprehensive microsimulation model for the US population to estimate the lifetime costs (from a healthcare payer perspective), health gains, and QALYS of expanding non-surgical periodontal treatment and lifetime maintenance coverage to 88%, compared to current coverage of 27% for patients with both periodontitis and type 2 diabetes. The model incorporated the cost, mortality, and quality of life impact of periodontal treatment on changes to several systemic disease risks: type 2 diabetes, periodontal disease, type 2 diabetes-related complications (nephropathy, neuropathy, and retinopathy), and cardiovascular disease (CVD) risks (myocardial infarction, stroke). The model predicted a 34% reduction in tooth loss, and 21% reduction in microvascular diabetes-related complications, leading to mean (95% credible intervals from simulations) net savings (2019 USD) to healthcare payers of USD 5904 (USD 5769 to USD 6039) per person and mean gains of 0.6 (0.5 to 0.6). The overall finding of the study was that expanding periodontal treatment among patients with diabetes and periodontitis was thus highly cost-effective due to modelled improved glycaemic control. However, there was substantial uncertainty surrounding the magnitude of cost savings that could be achieved, depending on assumptions about the true cost of initial and maintenance treatments, adherence rates, and the size of treatment effect on HbA1c.

In summary, the evidence available from existing studies, in particular two decision analysis models, indicates that there is potential for non-surgical periodontal treatment to be a cost-effective use of healthcare payer resources for patients with type II diabetes and periodontitis. However, the four economic evaluations were not quality assessed and there are several areas of uncertainty, which precludes definitive conclusions being drawn about the cost-effectiveness of periodontal treatment for patients with both diabetes and periodontitis.

DISCUSSION

Summary of main results

We found evidence to demonstrate that the treatment of periodontitis using subgingival instrumentation improves glycaemic control in people with diabetes, with a mean absolute reduction of 0.43% (4.7 millimoles per mole (mmol/mol)) in HbA1c (glycated haemoglobin) at 3 to 4 months, 0.30% (3.3 mmol/mol) at 6 months, and 0.50% (5.4 mmol/mol) at 12 months, when compared to no treatment or usual care. The certainty of the body of evidence for this finding was assessed as moderate (Summary of findings 1).

Adverse effects of periodontal treatments were rarely evaluated and so we cannot draw any reliable conclusions about any possible harm the interventions could cause.

The subgingival instrumentation interventions seemed to successfully treat periodontitis, with or without adjuncts such as oral hygiene instruction and antimicrobials, though residual inflammation remained in some cases. Results showed benefit from periodontal treatment at all time points for a range of indicators, i.e. plaque index, gingival index, clinical attachment level, bleeding on probing, and probing pocket depth.

We are unable to draw reliable conclusions about the impact of periodontal treatment on quality of life or diabetic complications because data were very limited.

Cost implications were not assessed in the included studies; however, we undertook additional searches to identify other types of evidence and prepared a brief economic commentary, which concluded that treating periodontitis in diabetic patients may reduce overall healthcare costs for these patients.

Overall completeness and applicability of evidence

The results of this review are widely applicable as the included studies assessed a varied population with a wide age range, a good balance of males and females, and varied glycaemic control (HbA1c thresholds) who were using different forms of antidiabetic therapy. It should be noted, however, that the studies focused almost exclusively on people with type 2 diabetes mellitus, and most studies took place in secondary care (hospital) settings.

Only one study included surgery (D'Aiuto 2018), and this was used only for a subset of patients who had already received non-surgical subgingival instrumentation as part of the intervention protocol.

Participation in the trials might have resulted in patients monitoring their blood sugars and taking better care of their health by complying with their medication more than they normally would. This might have resulted in an overestimation of the benefit of periodontal interventions due to potential Hawthorne effect impact (McCambridge 2014).

We have not been able to explore in this review whether there is a differential effect depending on type of diabetes or the level of metabolic control at baseline. This may be better addressed in part two of the review, which compares different approaches to periodontal treatment head-to-head.

The primary outcome of this review was HbA1c, which is one measure for diabetes that is widely used, although there are others.

We were able to conduct subgroup analyses based on the treatment setting (hospital, community, or primary care), although due to few studies not being conducted in a hospital setting, the findings were inconclusive. Subgroup analyses to explore the impact of adding an antimicrobial to subgingival instrumentation were also inconclusive.

We found very limited evidence on the impact on quality of life and no information on diabetes complications. Furthermore, adverse events were seldom reported. A programme of research could be undertaken to determine which outcomes are most important to people with diabetes (Raval 2021).

Cost implications were not reported in the studies. We conducted a brief economic commentary (BEC) that found four relevant economic evaluations and concluded there are potential cost savings, but the evidence is uncertain. Users of this review can judge the extent to which the methods and principal findings of the four studies in the BEC apply to their own healthcare system and setting.

Quality of the evidence

The certainty of the body of evidence was moderate for our main outcome, downgraded from high due to risk of bias. We did not assess the certainty of evidence for secondary outcomes. Although there was heterogeneity in the main analyses, we considered the consistent effect across time points to outweigh any concerns about this, and so we did not downgrade for inconsistency.

All studies were at high risk of performance bias because it is not possible to blind participants and personnel in these types of trials. We conducted sensitivity analysis for the main outcome, HbA1c, based on two trials at overall low risk of bias (low risk for selection, attrition, reporting, and other bias domains). We did not consider the result of this to undermine our main findings.

Publication bias was not suggested by our funnel plot for HbA1c at 3 to 4 months.

In terms of potential costs, our brief economic commentary concluded that the evidence is very uncertain. Our certainty in the evidence could be increased by work to derive more precise estimates of the true opportunity costs of periodontal treatment and maintenance therapy delivery, not only the value of claims reimbursement, but also the opportunity cost of time, equipment, and consumables to dental care providers. Long-term adherence to treatment does not appear to be well understood, and could be explored further, both in terms of adherence parameters and the proportion of those who adhere to treatment that can achieve the desired effect in terms of HbA1c reductions.

Potential biases in the review process

We did not conduct a separate search for adverse events.

One study included regular use of Listerine over a 3-week period in the treatment group (Bukleta 2018). Although Listerine may have antimicrobial activity, we did not include it in our third subgroup, which focused on the usual periodontists' choice of mouthwash, chlorhexidine. As we could have chosen to include this with the chlorhexidine mouthrinse studies, we conducted one post hoc sensitivity analysis removing Bukleta 2018 altogether, and another moving it to the antimicrobial mouthrinse subgroup, which confirmed that the choice of how to categorise Bukleta 2018 was immaterial.

One review author (Ambrina Qureshi (AQ)) was a principal investigator for one of the studies included in this review (Qureshi 2021). This author had no involvement in the selection, extraction, or assessment of primary data from this study.

Agreements and disagreements with other studies or reviews

This updated review includes literature up to 7 September 2021 so provides the most up-to-date evidence from randomised controlled trials evaluating the impact of periodontal treatment on people with both periodontitis and diabetes. It consolidates the findings of other evidence syntheses conducted over the intervening years since the last iteration of our review. These other published systematic reviews include different combinations of studies, but concur that periodontal treatment with subgingival instrumentation is likely to lead to an absolute reduction in HbA1c of between 0.26% to 0.56% in the short term, when compared with no intervention or usual care (Baeza 2020; Cao 2019; Chen 2021; Jain 2019; Teshome 2017). Although one systematic review with network meta-analysis ranked one treatment protocol higher than others (subgingival instrumentation + photodynamic therapy + doxycycline) (Cao 2019), overall there seems to be consensus that there is currently no evidence that the use of adjuncts such as antimicrobials significantly increase the benefits of subgingival instrumentation (Cao 2019; Teshome 2017; Yap 2019). Some systematic reviews have found that participants with higher HbA1c scores at baseline are more likely to benefit from periodontal treatment (Cao 2019; Chen 2021).

AUTHORS' CONCLUSIONS

Implications for practice

There is moderate-certainty evidence that the treatment of periodontitis by subgingival instrumentation improves glycaemic control in people with diabetes, with a mean absolute reduction in HbA1c (glycated haemoglobin) of 0.43% (4.7 millimoles per mole (mmol/mol)) at 3 to 4 months, maintained up to 12 months. There is insufficient evidence to draw reliable conclusions about the

potential of periodontal treatment to cause adverse effects or to impact quality of life or diabetic complications.

Implications for research

We think it may be unnecessary to conduct future trials comparing periodontal treatment versus no treatment/usual care, and that this would constitute research waste. Exploration of different patient characteristics and possible adverse effects are most appropriately studied within observational research. Specific head-to-head comparisons, including different periodontal treatment modalities, specialist-led care versus treatment provided by non-specialists and different treatment adjuncts will be evaluated in part two of this review. Future research could consider costs and how the delivery of care for patients with diabetes is best integrated across healthcare settings. Such studies might include a variety of research designs, depending on the question to be addressed, ideally with co-operative working between researchers with dental/periodontal and medical backgrounds, and with patient involvement in study design and conduct.

ACKNOWLEDGEMENTS

For this updated review (2022), we thank Cochrane Oral Health, particularly Anne Littlewood (who devised search strategies and ran the searches), Luisa M Fernandez Mauleffinch, and Anne-Marie Glenny; peer reviewers Professor Philip Preshaw (School of Dentistry, University of Dundee, UK) and Pia-Merete Jervøe-Storm (Department of Periodontology, Operative and Preventive Dentistry, Center for Dental and Oral Medicine, University Hospital Bonn, Germany); translator Sinval A Rodrigues Junior; and trial authors who provided additional information about their studies, P Kaur Khanuja (Kaur 2015), E Mauri and J López (Mauri-Obradors 2018).

Cochrane Oral Health supported the authors in the development of this review update. The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision) and Editor (provided feedback on submitted draft to prepare for peer review): Anne-Marie Glenny, Co-ordinating Editor, Cochrane Oral Health, The University of Manchester, UK.
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, conducted editorial policy checks) and Copy Editor (copy edited final draft according to Cochrane style manual): Luisa M Fernandez Mauleffinch, Managing Editor, Cochrane Oral Health, The University of Manchester, UK.
- Information Specialist (checked accuracy of search sections of the review): Anne Littlewood, Information Specialist, Cochrane Oral Health, The University of Manchester, UK.

For earlier versions of this review, we thank Cochrane Oral Health, specifically, Anne Littlewood, Laura MacDonald**,** Luisa M Fernandez Mauleffinch, and Anne-Marie Glenny; Cochrane Oral Health translators Chunjie Li, Andreas Neudecker, and Farhad Shokraneh; and peer reviewers Rahul Alam, Deborah Matthews, Didac Mauricio, and Hugo Pinto. We thank the trial authors who provided unpublished information that allowed more thorough appraisal of studies: Elena Firkova (Yun 2007), Judith Jones (Jones 2007), Sayaka Katagiri (Katagiri 2009), Panagiotis Koromantzos (Koromantzos 2011), Shaila Patil Kothiwale (Kothiwale 2013), Elif Unsal (Kiran 2005), and Jean-Noel Vergnes (Calbacho 2004; Vergnes 2018).

We gratefully acknowledge the contributions of Brian Stevenson, Susan Furness, David Moles, and Edward Mills as authors on earlier versions of this review.

Particular thanks are expressed by Terry Simpson to Richard Ibbetson for his personal support and guidance during this review's initial conception.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Artese 2015

Study characteristics	
Methods	**Trial design:** 2-arm RCT
	Location: São Paulo, Brazil
	Setting: not reported

Artese 2015 *(Continued)*

	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 yrs of age, confirmed diagnosis of T2DM for a period of over 3 yrs, generalised severe chronic periodontitis (number of PPD sites ≥ 30%, CAL > 4 mm, and BOP), and ≥ 15 teeth **Exclusion criteria:** pregnant women, smokers, people with BMI > 35 kg/m^2, or those who had received periodontal therapy, systemic antibiotic, or oral antiseptic therapy 6 mths prior to the study **Age at baseline (yrs):** Gp A 54.4 (SD 5.8), Gp B 52.0 (SD 3.3) **Sex (M:F):** unclear (authors report Gp A 56.3% female, Gp B 52.0% female) **Tobacco use:** none (exclusion criteria) **Alcohol consumption:** not reported **Diabetes type:** T2DM, 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 mths
Interventions	**Comparison: 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 (SRP) (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 anaesthesia (3% prilocaine with felypressin), in two appointments lasting ~ 120 minutes each") All participants given OHI every month "Periodontal therapy was carried out by an experienced periodontist" **Duration of follow-up:** 6 mths
Outcomes	HbA1c, GBI, VPI, PPD, CAL, BOP. Stratification results presented for PD and CAL. Serum levels of interleukin (IL)-6, IL-17A, IL-8, TNF-α, monocyte chemoattractant protein (MCP)-1 enzyme-linked immunosorbent assay (ELISA) Measured at 6 mths
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

Artese 2015 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer random number generator
Allocation concealment (selection bias)	Low risk	Allocated by sequentially numbered, sealed, opaque envelopes
Blinding of participants	High risk	Not feasible
Blinding of clinical operator	High risk	Not feasible
Blinding of periodontal outcome assessor	Low risk	Clinical examinations performed by 2 blinded and calibrated examiners
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for Quote: "All patients selected for analysis in the present study completed 6 months of the clinical trial"
Selective reporting (reporting bias)	High risk	HbA1C was analysed but numerical results were not reported other than in a graph from which data could not be extracted
Other bias	Low risk	None apparent

Bukleta 2018

Study characteristics

Methods	**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 **Setting:** hospital **Number of centres:** 1 **Recruitment period:** 2015 to 2016 **Funding source:** Slovenian Human Resources Development and Scholarship Fund (SHRDSF) for scholarship for Dr Dashnor Bukleta
Participants	**Inclusion criteria:** age 30 to 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 periodontal disease with at least 1 site with a PD ≥ 5 mm, 2 teeth 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 mths 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

Bukleta 2018 *(Continued)*

	Age at baseline (yrs): 59.49 (SD 10.82) across both gps **Sex (M:F):** 50:50 across both gps **Tobacco use:** 88 across both gps (also weight, BMI, and height recorded as well as oral therapy and insulin) **Alcohol consumption:** not reported **Diabetes type:** T2DM **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) **Other clinical investigations:** hs-CRP **Number randomised:** 100 diabetic participants **Number evaluated:** 100 (50 in each gp) at 3 mths
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 Planing (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 mths
Outcomes	**Primary:** HbA1c, fasting blood samples for the measurement of hs-CRP **Secondary:** mean PD, mean attachment level, PI, BOP Measured at baseline and 3 mths 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”

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentioned
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants	High risk	Open label
Blinding of clinical operator	High risk	Open label

Bukleta 2018 *(Continued)*

Blinding of periodontal outcome assessor	High risk	Trial registration states no masking
Incomplete outcome data (attrition bias) All outcomes	High risk	24 lost to follow-up. Missing data on mean attachment level in control group. Not clear if intention-to-treat analysis was used
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	None apparent

Calbacho 2004

Study characteristics	
Methods	**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 to 60 yrs, diagnosis of T2DM with poor metabolic control of diabetes and moderate chronic marginal periodontitis diagnosis without treatment of this disease from 1 yr 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 T2DM **Duration since diabetes diagnosis:** both groups 10.0 yrs (SD 3.4) **Metabolic control:** mean HbA1c % at baseline Gp A 9.70 (SD 2.90), Gp B 10.40 (SD 2.30) (P = 0.23) **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 vs OHI**

Calbacho 2004 *(Continued)*

	Gp A: (n = 12) "conventional" periodontal treatment + doxycycline 100 mg daily for 10 days Gp B: (n = 12) OHI only **Duration of follow-up:** 4 mths
Outcomes	**Primary:** HbA1c, at baseline, 2 and 4 mths **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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	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 risk	Not reported
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed. ITT analysis
Selective reporting (reporting bias)	High risk	Secondary outcomes only reported as P values (no means or SDs provided despite repeated email request)
Other bias	Unclear risk	Insufficient description in abstract and from author's comments to make a judgement

Chen 2012

Study characteristics	
Methods	**Trial design:** 3-arm, single-centre, parallel-design RCT **Location:** Guangzhou, China **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 T2DM > 1 yr; no change in TP in the previous 2 mths; no major diabetic complication (e.g. CHD); diagnosis of chronic periodontal disease (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 periodontal disease; systemic antibiotic administration in last 3 months; pregnancy or lactation; refusal of written consent; active infections other than periodontitis; periodontal treatment in last 12 mths **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:** T2DM **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), hs-CRP (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 vs SRP + OHI (x 3) + supragingival prophylaxis vs 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 mths check-ups) + subgingival debridement (at 3 mths) 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 mths check-ups) + supragingival prophylaxis (at 3 mths; no intervention in deep periodontal pockets)

Chen 2012 *(Continued)*

	Gp C (n = 44): no intervention (delayed treatment until completion of study) **Duration of follow-up:** 6 mths, with interim readings taken at 1.5 and 3 mths
Outcomes	**Primary:** HbA1c (measured at baseline, 1.5, 3, and 6 mths) **Secondary:** PI, BOP, mean PD, sites with PD = 4 to 5 mm, sites with PD ≥ 6 mm and mean CAL (all measured at 1.5, 3, and 6 mths)
Notes	**Sample size calculation:** a priori calculation assuming SD of 1% at 80% power – approximately 53 per gp **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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "...computer-generated list of random numbers prepared by statistician"
Allocation concealment (selection bias)	Unclear risk	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 risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for with reasons provided. Per-protocol analysis
Selective reporting (reporting bias)	Low risk	No evidence of reporting bias
Other bias	Low risk	None apparent

D'Aiuto 2018

Study characteristics

Methods	**Trial design:** parallel-group, single-blinded (examiner) RCT

D'Aiuto 2018 *(Continued)*

	Location: London, UK **Setting:** hospital **Number of centres:** 1 **Recruitment period:** October 2008 to October 2012 (4 yrs) **Funding source:** Diabetes UK and UK NIHR
Participants	**Inclusion criteria:** type 2 diabetes (WHO diagnostic criteria) for 6 mths or longer, moderate to severe periodontitis (at least or more 20 periodontal pockets with PPDs 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 wks with drugs known to affect periodontal tissues, chronic systemic antibiotic treatment, pregnancy or lactation **Age at baseline (yrs):** Gp A 58.2 (SD 9.7), Gp B 55.5 (SD 10.0) **Sex (M:F):** Gp A 82:51, Gp B 83:48 **Tobacco use:** 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:** T2DM **Duration since diabetes diagnosis (yrs):** Gp A 8.3 (SD 7.4), Gp B 8.7 (SD 8.4) **Metabolic control:** mean baseline HbA1c % Gp A 8.1 (SD 1.7), Gp B 8.1 (SD 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, 6, and 12 mths **Numbers lost to follow-up:** 8 at 2 mths (Gp A 5, Gp B 3); 20 at 6 mths (Gp A 12, Gp B 8) and 12 mths (Gp A 12, Gp B 8)
Interventions	**SRP vs usual care** **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, 2/6/9/12 mths) subgroup: patients with < 20% plaque scores + > 1 **Gp B (n = 131):** control - essential dental care + OHI + compromised teeth removal (baseline only?); full-mouth supragingival scale and polish (at baseline, 2/6/9/12 mths) **Duration of follow-up:** 12 mths
Outcomes	**Primary:** HbA1c **Secondary:** recession of gingival margin relative to cementoenamel junction at 6 sites per tooth Gingival indices: gingival bleeding on probing; gingival probing depth Periodontal lesions with probing depths of more than 4 mm

D'Aiuto 2018 *(Continued)*

	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 participants per gp for 1% (SD 2.1) difference in HbA1c at 12 mths (assuming 10% lost to follow-up) Much of the data not in the main paper but in an appendix **Conflicts of interests:** authors declare no conflict **Trial ID:** ISRCTN83229304 (retrospectively registered in 2010) Funder stated to have had role in study design, but not in data collection, analyses, interpretation, write-up Changes in prescribed medications were similar between the groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	Quotes: “Patients were allocated to clinicians in a random order” - 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 or who by and whether windowless and sealed envelopes
Blinding of participants	High risk	Participants were not blinded to group allocation
Blinding of clinical operator	High risk	Dental staff delivering treatment were not blinded to participant group
Blinding of periodontal outcome assessor	High risk	Periodontal assessors not blinded Quote: "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 risk	Dropout relatively low - 8 at 2 mths (Gp A 5, Gp B 3); 20 at 6 mths (Gp A 12, Gp B 8) and 12 mths (Gp A 12, Gp B 8)) ITT analyses undertaken
Selective reporting (reporting bias)	Unclear risk	Many assessments presented in less accessible appendix publication
Other bias	Low risk	None apparent. Funder stated to have had role in study design, but not in data collection, analyses, interpretation, write-up

Das 2019

Study characteristics	
Methods	**Trial design:** parallel-group, 3-arm RCT **Location:** Regional Dental Hospital and Medical College, Guwahati, India **Setting:** hospital **Number of centres:** 2 **Recruitment period:** study performed between February 2009 and September 2010 **Funding source:** nil **Aim:** to assess the use of doxycycline in adjunct to periodontal therapy on the glycaemic levels for chronic periodontitis patients with T2DM
Participants	**Inclusion criteria:** T2DM with moderate to severe periodontitis (where 30% of teeth have ≥ 4 mm 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 treatment during last 6 mths, antibiotics last 3 mths, < 20 teeth, allergic to tetracycline, pregnant and lactating mothers, consuming any tobacco **Age at baseline (yrs):** Gp A 38 (SD 11), Gp B 42 (SD 13), Gp C 40 (SD 12) **Sex (M:F):** Gp A 10:7, Gp B 8:9, Gp C 11:6 **Tobacco use:** all non-smokers **Alcohol consumption:** not reported **Diabetes type:** T2DM **Duration since diabetes diagnosis (yrs):** not reported **Metabolic control:** mean HbA1c % Gp A 7.58 (SD 0.89), Gp B 8.42 (SD 1.27), Gp C 8.35 (SD 0.96) **Other clinical investigations:** metabolic parameters FPG, and PPG **Number randomised:** total 51 (17 per gp) **Number evaluated:** 51 at 3 mths (17 per gp)
Interventions	**Comparison: SRP vs SRP and doxycycline vs no periodontal treatment till 3 mths** Gp A (SRP): OHI and full mouth SRP (n = 17) Gp B (SRP + doxycycline): same as Gp A plus 16 doses of doxycycline of 100 mg (n = 17) Gp C (control): no treatment control (n = 17) **Duration of follow-up:** 3 mths
Outcomes	PPD, CAL, PI, GI, and metabolic parameters (HbA1c, FPG, 2-hour PPG) Evaluated at baseline (day 0) and after 3 mths (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 ($p<0.05$)"

Das 2019 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...randomly categorised into 3 groups by single investigator using block randomisation"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	High risk	The different interventions would be apparent to the participants
Blinding of clinical operator	High risk	The different interventions would be apparent to the operators
Blinding of periodontal outcome assessor	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All data reported in full
Other bias	Low risk	None apparent

El-Makaky 2020

Study characteristics	
Methods	**Trial design:** parallel-group, 2-arm RCT **Location:** Periodontology Department, Tanta University, Egypt **Setting:** hospital **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 yrs, HbA1c level 7% to 9%, no changes in diabetes treatment over previous 3 months, 40 to 70 yrs old, minimum of 6 teeth excluding third molars. CAL and PD ≥ 4 mm in more than 30% of sites, diagnosis with chronic periodontitis, perio diagnosis based on 4 teeth with at least 1 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 mths, allergy to metronidazole and amoxicillin **Age at baseline (yrs):** Gp A 53 (SD 7), Gp B 52 (SD 7) **Sex (M:F):** Gp A 18:26, Gp B 20:24

El-Makaky 2020 *(Continued)*

	Tobacco use: all non-smokers **Alcohol consumption:** not reported (alcoholics excluded) **Diabetes type:** T2DM **Duration since diabetes diagnosis (yrs):** at least 5 **Metabolic control:** mean HbA1c % Gp A 8.12 (SD 0.74), Gp B 8.21 (SD 0.71) **Other clinical investigations:** not reported **Number randomised:** total 88 (44 per gp) **Number evaluated:** 88 at 3 mths (44 per gp)
Interventions	**Comparison: SRP + antibiotics + OHI vs delayed treatment** Gp A (SRP + antibiotics): OHI, full mouth SRP, metronidazole 400 mg 3x daily for 2 wks and amoxicillin 500 mg 3x daily for 2 wks (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 treatment (n = 44) **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HbA1c **Secondary:** periodontal attachment level (CAL mm); BOP (% sites); visible plaque index (Y/N); PPD mm Measured at baseline and 3 mths
Notes	**Sample size calculation:** not reported **Adverse effects:** first sentence of Results - "None of the patients in the test group reported significant side effects after periodontal therapy"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “...closed envelopes were used by the study coordinator to randomly allocate the patients to the test and control group, using a 1:1 allocation ratio”
Allocation concealment (selection bias)	Unclear risk	Quote: “This 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 risk	The different interventions would be apparent to the participants
Blinding of clinical operator	High risk	The different interventions would be apparent to the operators
Blinding of periodontal outcome assessor	Low risk	Quotes: "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 risk	No dropouts

El-Makaky 2020 *(Continued)*

Selective reporting (reporting bias)	Low risk	All data reported in full
Other bias	Low risk	None apparent

Engebretson 2013

Study characteristics	
Methods	**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 to 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 < -0.12 t-test for HbA1c was -0.37, consequently monitoring board recommended cessation of recruitment **Funding source:** 2 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 mths); an HbA1c value between 7% to < 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 mths; 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 yr); diabetes-related emergency in prior 30 days; NSAID use (> 7 days in prior 2 mths. 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 (kg):** Gp A mean 99.5 (SD 24.3), Gp B mean 97.5 (SD 21.7) **BMI:** Gp A 34.7 (SD 7.5), Gp B 34.2 (SD 6.7) **Alcohol consumption:** not reported **Diabetes type:** T2DM

Engebretson 2013 *(Continued)*

	Duration since diabetes diagnosis (yrs): Gp A mean 12.3 (SD 8.2), Gp B 11.3 (SD 8.4) **Metabolic control:** largely fair-poor mean HbA1c at baseline 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 179 Gp A: no diabetes medications 7; oral agents only 117; insulin only 40; combination of medications 93 Gp B: no diabetes medications 4; oral agents only 127; insulin only 40; combination of medications 86 **Other clinical 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 14 Gp 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 mths: Gp A 257, Gp B 257 Per-protocol analysis (all outcomes – all participants with HbA1c data at 6-mth visit): Baseline: Gp A 240, Gp B 235 3 mths: Gp A 233, Gp B 227 (missed 3-mth visit: Gp A 6, Gp B 7. Periodontal data missing: Gp A 1, Gp B 1) 6 mths: 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) vs OHI (x 3)** Gp A (n = 257): SRP (at baseline, 3 and 6 mths: 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 mths comprised of a single 1 h session each time) + OHI and provision of 0.12% chlorhexidine gluconate oral rinse (0.5 oz twice daily for 2 wks), toothbrush, toothpaste, and dental floss Gp B (n = 257): OHI at baseline, 3, and 6 mths (followed by offer of SRP after 6-mth visit) **Duration of follow-up:** 6 mths
Outcomes	**Primary:** HbA1c **Secondary:** GI, BOP, PPD, and CAL Measured at baseline, 3, and 6 mths
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

Engebretson 2013 *(Continued)*

Overall: Black 146; White 280; Hispanic 166; other 88
Gp A: Black 76; White 140; Hispanic 81; other 41
Gp 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, from Zimmer 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	Quotes: "...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 risk	Quotes: "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

Engebretson 2013 *(Continued)*

		unlikely that the provision of a sham treatment would adequately mask control participants either"
Blinding of clinical operator	High risk	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 risk	Quote: "Periodontal examiners and laboratory personnel who performed the HbA_{1c} analyses were masked to treatment group assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	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 risk	All reported (albeit via supplementary material available online). Adverse events reported
Other bias	Unclear risk	Conflict of interests declaration reported for all authors except lead author

Felipe 2015

Study characteristics	
Methods	**Trial design:** 2-arm RCT **Location:** University Hospital Pedro Ernesto/UERJ, Brazil **Setting:** hospital **Number of centres:** 1 **Recruitment period:** 14 mths (October 2013 to December 2014) **Funding source:** none declared
Participants	**Inclusion criteria:** diagnosis of T2DM; minimum treatment time for DM of 1 yr; severe chronic periodontitis (AAP); minimum 10 teeth present; at least 2 sites with PD ≥ 6 mm and 2 sites with CAL ≥ 5 mm **Exclusion criteria:** periodontal or antibiotic therapy within the last 6 months; presentation with rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, or Crohn's disease **Age at baseline (yrs):** Gp A 58.1 (SD 8.4), Gp B 54.1 (SD 9.9) (P = 0.26) **Sex (M:F):** Gp A 11:10, Gp B 14:6 (P = 0.2) **Tobacco use:** not reported **Alcohol consumption:** not reported **Duration since diabetes diagnosis:** not reported **Number of standing teeth:** Gp A 21.4 (SD 3.7), Gp B 18.2 (SD 4.9) **Metabolic control:** mean HbA1c % Gp A 7.1 (SD 1.9), Gp B 8.2 (SD 2.3) **Other clinical investigations:** periodontal clinical examination **Number randomised:** 41 (initially 42 (21 per group), but 1 participant did not attend baseline exam and was excluded from study)

Felipe 2015 *(Continued)*

	Number evaluated: 41 for most outcomes, but only 36 (18 per group) for HbA1c
Interventions	**Comparison: SRP vs no treatment** Gp A (n = 21): oral hygiene advice + non-surgical supragingival and subgingival scaling under local anaesthesia Gp B (n = 20): no treatment up to the 90th day of study **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HbA1c **Secondary:** clinical periodontal parameters (PD, CAL, BOP, PI), inflammatory markers (interleukin -1β and -6, TNF-α, resistin, leptin, and adiponectin), other markers (total cholesterol, 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 Data extraction by translator Professor Sinval A Rodrigues Junior

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Participants were randomly allocated to groups” – no description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants	High risk	No description, but not possible
Blinding of clinical operator	High risk	No description, but not possible
Blinding of periodontal outcome assessor	High risk	Quotes: “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 risk	Quote: “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 Unclear if ITT analysis undertaken
Selective reporting (reporting bias)	Low risk	All outcome data reported for both groups
Other bias	Unclear risk	Hypertension, heart disease, smoking habit, family history, medicine use and lifestyle data unreported

Gay 2014

Study characteristics	
Methods	**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 T2DM; possessing HbA1c value > 6.5% at screening (although initial values of 5.7% to 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 mths; systemic antibiotics within 6 mths 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 T2DM **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) vs OHI**

Gay 2014 *(Continued)*

	Gp A (n = 77): OHI at baseline (including modified Bass technique, interdental brush/floss use), + SRP 4 to 6 wks 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 to 6 wks later **Duration of follow-up:** 4 months
Outcomes	**Primary:** HbA1c (at baseline and 4 mths) **Secondary:** BOP, PD, and CAL (at baseline and 1 mth)
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	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 risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	High risk	All data (including baseline) only presented for evaluated (n = 126) participants, 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)

Gay 2014 *(Continued)*

		Per-protocol analysis
Selective reporting (reporting bias)	Unclear risk	All initially stated outcomes reported on in results/tables, albeit only including those evaluated
Other bias	Low risk	No other apparent biases

Jones 2007

Study characteristics	
Methods	**Trial design:** 2-arm, multicentre, parallel-design RCT (at 4 mths) **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 to 16 mth study **Exclusion criteria:** grave medical or psychiatric illness or severe immunocompromised (e.g. 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 T2DM 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:** 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

Jones 2007 *(Continued)*

Interventions	**Comparison: SRP + doxycycline + chlorhexidine rinse vs usual care** Gp A (n = 98): SRP + doxycycline (100 mg qid for 14 days) + chlorhexidine rinse (0.12% twice daily for 4 mths) Gp B (n = 95): usual care (described only as "usual medical and dental care") **Duration of follow-up:** 4 mths
Outcomes	**Primary:** change in HbA1c (not fully reported) **Secondary:** GI, GR
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	See above
Blinding of participants	High risk	Participants knew which group they were allocated to
Blinding of clinical operator	High risk	Quote: "...by seeking physicians' concurrence, in essence we notified each participant's primary care provider that his or her patient's diabetes was under

Jones 2007 *(Continued)*

		poor control. Because of this notification,some providers likely became more aggressive in treating these patients"
Blinding of periodontal outcome assessor	Low risk	Quote: "The study examiner...did not know to which study group participants were assigned"
Incomplete outcome data (attrition bias) All outcomes	High risk	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 dropout 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 risk	No mean HbA1c values at 4 mths 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 participants (varies for each characteristic) (n = 154 to 165), rather than those randomised (n = 193) 1 participant from each group not accounted for
Other bias	High risk	Baseline differences with respect to smoking, history of stroke, transient ischemic attacks, diabetes with nephropathy Unclear what usual care comprised

Kapellas 2017

Study characteristics	
Methods	**Trial design:** 2-arm RCT **Location:** Australia's Northern Territory **Setting:** not reported **Number of centres:** 4 locations **Recruitment period:** June 2010 to January 2012 (with final annual assessment in December 2012) **Funding source:** the Perio-Cardio study was funded by 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 yrs or older without a previous history of cardiovascular disease, a minimum of 5 natural teeth and moderate/severe periodontitis defined using the joint CDC-AAP case definition **Exclusion criteria:** individuals receiving periodontal treatment in the preceding 6 mths, those with cardiovascular disease history, rheumatic fever or any other medical condition requiring preventive an-

Kapellas 2017 *(Continued)*

	tibiotic prophylaxis, pregnant women, or people with clinically visible endodontic or orofacial infections **Age at baseline:** Gp A 45.5 (SD 10.9), Gp B 46.4 (SD 9.1) **Sex (M:F):** Gp A 18:17, Gp B 17:10 **Tobacco use:** smoker/ex-smoker/never Gp A 12/2/13, Gp B 7/6/3 **Alcohol consumption:** not recorded **Diabetes type:** T2DM **Duration since diabetes diagnosis:** not reported **Metabolic control:** HbA1c % Gp A 70.3 mmol/mol 8.6 (SD 4.4), Gp B 60.8 mmol/mol 7.7 (SD 4.0) **Other clinical investigations:** C-reactive protein (CRP)IL-6, total cholesterol, HDL-C, BMI, waist-to hip ratio **Number randomised:** 62 (Gp A 35, Gp B 27) **Number evaluated:** 44 at 3 mths (Gp A 24, Gp B 20)
Interventions	**Comparison: SRP vs delayed treatment** Intervention gp: single episode of non-surgical periodontal therapy comprising supragingival and subgingival scaling using hand instruments and ultrasonic device under local anaesthetic Control gp: delayed treatment (12 mths) Gp A (n = 35), Gp B (n = 27) **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HbA1c (data converted from mmol/mol to %) **Secondary:** gingival bleeding, PPD ≥ 4 mm, CAL ≥ 3 mm number of sites of each/total sites
Notes	**Sample size calculation:** post hoc power calculation for change in HbA1c at 3 mths using the 2 sample means feature of PROC POWER in SAS 9.3 for Windows, Cary, NC, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	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 risk	Stated that not blinded
Blinding of clinical operator	High risk	Stated clinicians not blinded
Blinding of periodontal outcome assessor	High risk	Stated dental clinicians not blinded. Inter-examiner kappa score 0.75, 95% CI 0.70 to 0.80

Kapellas 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	18 lost to follow-up Intervention: 11 (10 lost to follow-up, 1 withdrawn) Control: 7 (6 lost to follow-up, 1 moved away)
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Low risk	None apparent

Katagiri 2009

Study characteristics	
Methods	**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 to 75 yrs, HbA1c 6.5% to 10.0%; at least 11 remaining teeth, at least 2 pocket sites with PD 4 mm or more (indicated as mild to severe periodontitis), no periodontal treatment during the preceding 6 mths **Exclusion criteria:** severe diabetic complications; evidence of systemic diseases other than diabetes as a risk factor for periodontitis; systemic antibiotics during the preceding 3 mths; pregnancy or lactation; allergy to tetracycline; smoking; modifications in the treatment of diabetes during the preceding 2 mths **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:** T2DM **Duration since diabetes diagnosis:** Gp A: 11.3 yrs (SD 6.4), Gp B: 8.8 yrs (SD 7.5) **Metabolic control:** 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

Katagiri 2009 *(Continued)*

	Number randomised: 49 (Gp A 32, Gp B 17) **Number evaluated:** 49
Interventions	**Comparison: SRP + minocycline + OHI vs 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 mths. Additional periodontal treatment including instructions for brushing, supra- and subgingival 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 mths of intensive period periodontal treatment, all participants visited the respective medical and dental clinics at 1, 3, and 6 mths **Duration of follow-up:** 6 mths
Outcomes	**Primary:** HbA1c at 1, 3, and 6 mths **Secondary:** change in PPD at 1 mth (Delta PPD), change in BOP at 1 mth (Delta BOP) and intervention of periodontal treatment on the change in HbA1c at 6 mths
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated by envelope method" - method of sequence generation not described
Allocation concealment (selection bias)	High risk	Envelope method. Dentists knew the allocations to each group (from correspondence with the author)
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in outcome evaluation. ITT analysis

Katagiri 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	HbA1c not reported by group but details later supplied by the lead author
Other bias	Low risk	No other apparent biases

Kaur 2015

Study characteristics	
Methods	**Trial design:** double-blinded (operator and assessor), parallel, 5-arm RCT (stratified by poor and good glycaemic control) **Location:** Department of Periodontics and Oral Implantology, Rohtak, India **Setting:** hospital **Number of centres:** 1 **Recruitment period:** 23-mth duration (February 2010 to January 2012) **Funding source:** none
Participants	**Inclusion criteria:** receipt of treatment for at least 1 yr after T2DM diagnosis, aged 45 to 60 yrs, presence of ≥ 12 teeth (excluding third molars), no change in medication use (oral hypoglycemics/insulin/etc) in 2 mths 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 periodontal disease course, pregnancy, lactating, current/ex-smokers, major diabetic complications, use of systemic antibiotics in prior 3 mths, periodontal treatment in prior 6 mths **Age at baseline (yrs):** Gp A 51.82 (SD 5.85), Gp B 52.94 (SD 6.03) **Sex (M:F):** Gp A 22:28, Gp B 26:24 **Tobacco use:** "current or past smokers were excluded from our study" **Alcohol consumption:** not reported **Diabetes type:** T2DM **Duration since diabetes diagnosis (yrs):** Gp A 8.57 (SD 6.39), Gp B 7.05 (SD 4.43) **Mean HbA1c %:** Gp A 8.17 (SD 2.49), Gp B 7.87 (SD 2.56) **Other clinical investigations:** FPG, PPG **Number randomised:** 100 **Number evaluated:** 3 mths 100, 6 mths 100 **Attrition:** Gp A 5 lost to follow-up (non-attending), Gp B 4 lost to follow-up (non-attending)
Interventions	**Comparison: SRP versus delayed 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 mths

Kaur 2015 *(Continued)*

Outcomes	**Primary:** HbA1c **Secondary:** PI, GI, PPD, CAL, BOP Assessed at baseline, 3, and 6 mths
Notes	**Sample size calculation:** on the basis of an expected mean difference in HbA1c of approximately 0.4% between groups and SD 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 2-sided type 1 error of 5% **Adverse effects:** neither compliance nor adverse effects seem to have been assessed nor reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is stated to have taken place after exclusion for eligibility leaving 100 participants. Allocation was then done on the basis of HbA1c levels. From personal correspondence: "These patients were then further randomly allocated to either the treatment group...or the no-treatment group...(n = 50 each). Computer software was used to avoid a disparity. A number from 1-100 was assigned to patients according to their recruitment date"
Allocation concealment (selection bias)	Unclear risk	From personal correspondence: "As computer software was used for allocation, patients were numbered but they were not aware of the fact"
Blinding of participants	High risk	Not possible owing to differences in allocated interventions
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	Quotes: “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 risk	Quote: “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 risk	All assessed outcomes fully presented
Other bias	Low risk	None apparent

Kiran 2005

Study characteristics

Methods	**Trial design:** 2-arm, single-centre, parallel-design RCT **Location:** Turkey **Setting:** hospital

Kiran 2005 *(Continued)*

	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:** T2DM with HbA1c values of 6% to 8%; creatinine values of 1.4 mg/dl; liver function tests not > 3 x the normal range **Exclusion criteria:** major diabetic complications; systemic antibiotics administered within prior 3 mths; periodontal treatment within prior 6 mths **Sex (M:F**): overall: M18:F26, Gp A: M10:F12, Gp B: M8:F14 **Age at baseline (yrs):** overall 54.39 (SD 11.27); Gp A: mean 55.95 (SD 11.21); Gp B: mean 52.82 (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:** T2DM **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 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:** GR; FPG; 2-hour PPG; total cholesterol; triglyceride; HDL-C; LDL-C; microalbuminuria **Other medical conditions:** none reported **Number randomised:** 44 **Number evaluated:** 44
Interventions	**Comparison: SRP + OHI vs no/delayed treatment** 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 mths
Outcomes	**Primary:** HbA1c **Secondary:** PI, GI, PPD, CALs, and BOP Recorded at baseline, 1, and 3 mths
Notes	**Sample size calculation:** not reported **Data analysis:** ITT **HbA1c assessment method:** not reported **SES:** not reported

Kiran 2005 *(Continued)*

Adverse events: not reported

Conflict of interests: not reported

Clarification supplied by author

Teeth with periapical lesions were allocated additional treatment:

Gp A: 9 participants, 9 teeth: 4 extractions, 5 root canal treatment

Gp B: 5 participants, 5 teeth: 5 root canal treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	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 risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	Quote: "The examining investigator was unaware of group assignments"
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis, although participants 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 risk	All planned outcomes reported
Other bias	Low risk	None apparent

Koromantzos 2011

Study characteristics

Methods

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)

Koromantzos 2011 *(Continued)*

Participants	**Inclusion criteria:** T2DM with HbA1c levels ranging from 7% to 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 mths; non-surgical periodontal treatment during last 6 mths; surgical periodontal treatment over last 12 mths; current medication including usage of calcium channel blockers, phenytoin or cyclosporine; history of stroke or acute cardiovascular event over the past 12 mths; renal dysfunction determined by creatinine levels > 1.5 mg/dl or liver dysfunction defined as AT/ALT (alanine aminotransferase) levels > 2.5 times upper limit of normal **Age at baseline (yrs):** overall: mean 59.52 (SD 8.88), Gp A: mean 59.62 (SD 7.95), Gp B: mean 59.42 (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 (yrs):** overall 7.8 (SD 5.7), Gp A 7.76 (SD 4.3), Gp B 7.84 (SD 6.8) **Metabolic control:** mean 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/m^2):** 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-C, HDL-C **Number randomised:** 60 **Number evaluated:** 60 (4 lost to follow-up in Gp A, 3 in Gp B)
Interventions	**Comparison: SRP + OHI vs supragingival cleaning + OHI** Gp A (n = 30): OHI (at baseline, 1, and 3 mths) + SRP (2 sessions, 1 wk apart at baseline, using ultrasonic scaler and hand instruments, under local anaesthesia) + additional supportive SRP (at 1 and 3 mths) if required Gp B (n = 30): OHI (at baseline, 1, and 3 mths) + 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 mths
Outcomes	**Primary:** HbA1c (recorded at baseline, 1, 3, and 6 mths) **Secondary:** CAL, PPD, BOP, and GI (recorded at baseline, 1, 3, and 6 mths)
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

Koromantzos 2011 *(Continued)*

Adverse events: not reported

Conflict of interests: authors declare no conflict of interests

Gp A: 2/30 had extractions at baseline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	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 risk	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 risk	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 risk	Quote: "Patients were examined dentally through the course of the study by the same examiner"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Relatively low dropout, balanced across groups. All participants accounted for - ITT analysis
Selective reporting (reporting bias)	Unclear risk	No change data for triglycerides, total cholesterol, LDL-C, and HDL-C. 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 risk	None apparent

Kothiwale 2013

Study characteristics

Kothiwale 2013 *(Continued)*

Methods	**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, India **Recruitment period:** unknown **Funding source:** unknown
Participants	**Inclusion criteria:** aged 25 or older; known cases of T2DM (minimum duration of 2 yrs); 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 mths; antibiotic/anti-inflammatory drugs taken in prior 3 mths; have abnormal hepatic function; pregnant or lactating **Age at baseline (yrs):** Gp A: mean 57.7 (SD 8.61), Gp B: mean 56.4 (SD 11.53) **Sex (M:F):** overall: 32:18, Gp A: 15:10, Gp B: 17:8 **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 T2DM **Duration since diabetes diagnosis (yrs):** Gp A: mean 5.3 (SD 2.76); Gp B: 5.2 (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 community periodontal index (CPI) and loss of attachment (LOA) scores) **Other medical conditions:** not reported **Number randomised:** 50 (Gp A 25, Gp B 25) **Number evaluated:** not reported
Interventions	**Comparison: SRP + OHI vs no/delayed 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 mths
Outcomes	Change in HbA1c from baseline to 3 mths
Notes	**Sample size calculation:** not reported

Kothiwale 2013 *(Continued)*

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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Simply states 50 patients randomly assigned into 2 groups. No indication of method
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	No patient flow provided or any dropouts 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 risk	Planned outcomes reported on
Other bias	Unclear risk	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

Study characteristics

Methods

Trial design: preliminary report of a double-blinded, 3-arm, parallel RCT

Location: Community Healthcare Centre in Gwangjin-gu Public Health Centre, Seoul, Korea

Setting: community

Number of centres: 1

Lee 2020 *(Continued)*

	Recruitment: June 2013 to 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; HbA1c level ≥ 6.5%; non-smoking status; diagnosed with periodontitis **Exclusion criteria:** current abuse of alcohol or drugs; chronic liver disease including hepatitis; BMI ≥ 40 kg/m^2 Participants' age, BMI, HbA1c level, endotoxin level, interleukin-1 beta (IL-1β) level, and oral health status were recorded **Age at baseline (yrs):** Gp A SRP 71.15 (SD 8.61), Gp B SRPAT 72.45 (SD 8.20), Gp C Control 74.15 (SD 7.21) **Sex (M:F):** Gp A 10:10, Gp B 10:10, Gp C 10:10 **Smoking:** excluded **Alcohol consumption:** not reported **Diabetes type:** T2DM diagnosed as per WHO criteria **Duration since diabetes diagnosis:** not reported **Metabolic control:** mean HbA1c % at baseline Gp A 6.64 (SD 0.29), Gp B 6.68 (SD 0.23), Gp C 6.76 (SD 0.39) **Other clinical investigations:** BMI, serum IL-1β and endotoxin **Number randomised:** 75 (25 per gp) **Number evaluated:** 60 at 3 mths (20 per gp)
Interventions	**Comparison: SRP vs SRPAT vs control** Gp A SRP (n = 25): 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 wks, root planing was performed to remove the subgingival calculus. At 12 wks, patients were recalled to recheck their oral health status. If they required additional periodontal treatment, it was done at 12 wks. Gp B SRPAT (n = 25): 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 Gp C Control (n = 25): 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 **Duration of follow-up:** 3 mths
Outcomes	**Primary:** changes in HbA1c **Secondary:** interleukin-1 beta levels (IL-1β), serum endotoxin levels, PPD, CI, BOP (%)

Lee 2020 *(Continued)*

	Measured up to 12 wks 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	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 risk	Quote: "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 risk	None noted
Other bias	Low risk	None apparent

Li 2011

Study characteristics

Methods	**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 5-year Plan
Participants	**Inclusion criteria:** T2DM (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 yr

Li 2011 *(Continued)*

	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:** 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: SRP vs supragingival scaling vs 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 mths
Outcomes	**Primary:** HbA1c (at baseline, 6 wks, 3 and 6 mths) **Secondary:** PD, attachment loss, PI - 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

Bias	Authors' judgement	Support for judgement

Li 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote: "randomized" - no further information
Allocation concealment (selection bias)	Unclear risk	No information
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Quote: "blinded" - no further information
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information
Selective reporting (reporting bias)	Unclear risk	No information. Adverse effects not reported though stated as a secondary outcome
Other bias	Unclear risk	No way to verify if other biases exist due to translation of data extraction components

Mauri-Obradors 2018

Study characteristics	
Methods	**Trial design:** single-blinded, 2-arm RCT **Location:** not clear - University Hospital Barcelona, Spain **Setting:** hospital **Number of centres:** 3 **Recruitment period:** 6 mths **Funding source:** partially funded by a research grant from SEPA and by a research grant from the University of Barcelona
Participants	**Inclusion criteria:** T2DM (diagnosed at least 1.5 yrs prior the study) and generalised chronic periodontitis (Armitage 1999) at least 9 teeth present and > 30% of the probed gingiva with a depth and CAL ≥ 4 mm **Exclusion criteria:** antibiotic treatment during the previous 15 days or for periods > 10 days during the last 3 mths, non-surgical periodontal treatment within the past 6 mths, 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 (SD 11), Gp B 62 (SD 10) **Sex (M:F):** Gp A 17:25, Gp B 20:28 **Tobacco use:** smoker/ex-smoker/never Gp A 15/13/14, Gp B 3/22/23 **Alcohol consumption:** not reported **Diabetes type:** T2DM

Mauri-Obradors 2018 *(Continued)*

	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 mths, 79 at 6 mths
Interventions	**Comparison: SRP + OHI vs OHI** 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 mths
Outcomes	**Primary:** HbA1c, FPG **Secondary:** bacterial assessment, PPD, PI, GI Measured at baseline, 3, and 6 mths. HbA1c at 3 mths not reported or provided
Notes	**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 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	Single examiner blinded

Mauri-Obradors 2018 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11 dropouts (4 in Gp A, 7 in Gp B)
Selective reporting (reporting bias)	High risk	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 mths, although article implies it was measured
Other bias	Low risk	None apparent

Mizuno 2017

Study characteristics	
Methods	**Trial design:** 2-arm, single-blinded RCT **Location:** Japan **Setting:** hospital - Nephrology, Diabetology and Endocrinology Department of Okayama University Hospital **Number of centres:** 1 **Recruitment period:** April 2014 to March 2016 **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 mths 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 > 3 mm and 2 interproximal sites with PPD > 4 mm (not on the same tooth) or 1 site with PPD 5 mm **Exclusion criteria:** pregnancy, inappropriate status for the trials, such as a limited life expectancy and diabetes-related emergency, and receiving periodontal treatment in the prior 6 mths **Age at baseline (yrs):** 61.2 (SD 9.2) vs 62.8 (SD 12.1) **Sex (M:F)**: 28:9 **Tobacco use:** 7/37 **Alcohol consumption:** 14/37 **Diabetes type:** T2DM **Duration since diabetes diagnosis:** not reported **Metabolic control:** HbA1c > %: 7.5 (SD 1.7) vs 7.7 (SD 1.2) **Other clinical investigations:** glycated albumin, oxidative index **Number randomised:** 40

Mizuno 2017 *(Continued)*

	Number evaluated: at 3 mths 37 (Gp A 20, Gp B 17) (complete data for 31: Gp A 17, Gp B 14); at 6 mths 28 (Gp A 15, Gp B 13)
Interventions	**Comparison: SRP + OHI + supportive periodontal therapy vs OHI only** Periodontal treatment group (n = 20): non-surgical periodontal therapy, including SRP plus OHI, and consecutive supportive periodontal therapy at 3 and 6 mths Control group (n = 17): only OHI without treatment during the experimental period **Duration of follow-up:** 6 mths
Outcomes	**Primary:** change in HbA1c levels from baseline to 3 mths (also measured at 6 mths) **Secondary outcomes:** changes in oxidative stress balance (Oxidative-INDEX), the Diabetes Therapy-Related QOL and clinical periodontal parameters from baseline to 3 mths and baseline to 6 mths
Notes	**Trial ID:** Current Controlled Trials UMIN-ICDR UMIN 000013278 (registered 1 April 2014) - currently inaccessible online

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 1 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 risk	Not reported
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	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 risk	Attrition low and not a concern
Selective reporting (reporting bias)	Low risk	All expected outcomes reported
Other bias	Low risk	None apparent

Moeintaghavi 2012

Study characteristics

Methods	**Trial design:** 2-arm, single-centre, parallel-design RCT

Moeintaghavi 2012 *(Continued)*

	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 T2DM with HbA1c > 7%; no major complications of diabetes; controlled by oral hypoglycaemic agents (glybenglamide and metformin) but not insulin administration; no periodontal treatment or antibiotic administration in last 6 mths **Exclusion criteria:** presence of systemic diseases other than T2DM that could influence course of periodontal disease; 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 (yrs):** overall: 50.29 (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:** T2DM **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 vs no/delayed 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 mths
Outcomes	**Primary:** HbA1c (at baseline and 3 mths) **Secondary:** CAL, PPD, PI, and GI (at baseline and 3 mths)
Notes	**HbA1c assessment method:** Cobas Integra 700; Roche Diagnostics, Germany **Data analysis:** ITT **Conflict of interests:** not reported **Adverse events:** not reported

Moeintaghavi 2012 *(Continued)*

SES: not reported

Sample size calculation: a priori calculation based on Kiran 2005 and Rodrigues 2003 of 20 per group ($\alpha = 0.05$ and $\beta = 0.2$)

Trial ID: NCT01252082

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	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 risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	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 risk	Age differences not reported between group but by sex instead
Other bias	Low risk	No other apparent biases

Qureshi 2021

Study characteristics

Methods	**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 November 2017
Participants	**Inclusion criteria:** ≥ 2 interproximal sites having ≥ 5 mm PPD or ≥ 4 mm of CAL with at least 16 natural teeth on examination; having moderate to severe periodontitis; HbA1c level ≥ 6.5% and > 14% at base-

Qureshi 2021 *(Continued)*

	line 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) **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 2 mths of examination, other than low dose aspirin prescribed for cardiovascular disease (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:** fasting blood glucose **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 + 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 metronidazole 400 mg x 3 for 10 days along with warm salt water rinses for 3 to 5 days and OHI Gp B: received the same intervention as Gp A except metronidazole Gp C: OHI (delayed periodontal treatment) **Duration of follow-up:** 6 mths
Outcomes	Mean change in HbA1c (at 3 and 6 mths), fasting blood glucose, periodontal variables BOP, PPD, CAL (states L is loss in this paper) at 1 and 3 mths)
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

Bias	Authors' judgement	Support for judgement

Qureshi 2021 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random number table
Allocation concealment (selection bias)	Low risk	Quote: "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 risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	Quote: "...the periodontal examiners and biochemist were unaware of the type of intervention performed by the periodontal therapists"
Incomplete outcome data (attrition bias) All outcomes	High risk	Large dropout. Loss to follow-up of 76 of the 150 by month 6. ITT and PP analysis undertaken Quotes: "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 risk	Planned outcomes reported. ITT and PP analysis undertaken
Other bias	Low risk	None apparent

Raman 2014

Study characteristics	
Methods	**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 to 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 BOP

Raman 2014 *(Continued)*

	Exclusion criteria: systemic antibiotic use in prior 4 mths; pregnancy; current smoker; cardiovascular/cerebrovascular event in prior 12 mths; diabetes medication change during study; non-surgical periodontal therapy in prior 6 mths; surgical periodontal therapy in prior 12 mths **Age at baseline (yrs):** overall 56.2 (SD 8.1), Gp A: 57.7 (SD 9.9), Gp B: 54.6 (SD 6.2) **Sex (M:F):** overall 20:12, Gp A 11:4, Gp B: 9:8 **Tobacco use:** current smokers excluded from participation **Alcohol consumption:** not reported **Diabetes type:** all T2DM **Duration since diabetes diagnosis:** overall: < 7 yrs = 7 (21.9%), 7-12 yrs = 8 (25.0%), > 12 yrs = 17 (53.1%); Gp A: < 7 yrs = 4 (26.7%), 7-12 yrs = 4 (26.7%), > 12 yrs = 7 (46.7%); Gp B: < 7 yrs = 3 (17.6%), 7-12 yrs = 4 (23.5%), > 12 yrs = 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	**Comparison: SRP + OHI (x 3) + adjunctive chlorhexidine mouthrinse vs 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 per day 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 mths
Outcomes	**Primary:** HbA1c at baseline and 3 mths **Secondary:** PI, PPD, PAL (corresponds to CAL) at baseline, 2, and 3 mths
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

Raman 2014 *(Continued)*

Trial ID: NCT01951547

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 risk	Not reported
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	States "not double-blinded." Not reported further
Incomplete outcome data (attrition bias) All outcomes	High risk	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 risk	All planned outcomes fully reported on
Other bias	High risk	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

Study characteristics

Methods	**Trial design:** parallel-group, 2-arm RCT **Location:** Tirana, Albania **Setting:** not reported **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 mths, having diagnosis of periodontitis if CAL affected $\geq$ 2 non-adjacent teeth or buccal/oral CAL of $\geq$ 3 mm with pocketing of > 3 mm was detectable in $\geq$ 2 teeth

Rapone 2021 *(Continued)*

	Exclusion criteria: insulin dependent diabetes or higher chronic disease, smoking or consuming alcohol, antibiotics or anti-inflammatory drugs over previous 6 mths, pregnant or lactating women, having received periodontal treatment over previous year **Age at baseline (yrs):** Gp A 53 (SD 11); Gp B 56 (SD 7) **Sex (M:F):** Gp A 40:50; Gp B 36:54 **Tobacco use:** all non-smokers **Alcohol consumption:** not reported (alcoholics excluded) **Diabetes type:** T2DM **Duration since diabetes diagnosis (yrs):** at least 5 **Metabolic control:** mean HbA1c Gp A 8.08 (SD 1.97); Gp B 8.77 (SD 8.51) **SDerror in paper** **Other clinical investigations:** CRP- C-reactive protein **Number randomised:** total 187 (Gp A 93, Gp B 94) **Number evaluated:** 6 mths 180 (90 per group)
Interventions	**Comparison: SRP vs delayed treatment** Gp A (SRP) (n = 90): OHI, full mouth SRP delivered in 4 sessions of 45 min within 24 h Gp B (control) (n = 90): delayed periodontal treatment **Duration of follow-up:** 6 mths
Outcomes	**Primary:** HbA1c **Secondary:** periodontal attachment level (CAL mm); GI (% sites); visible plaque index; PPD mm Measured at baseline, 3, and 6 mths
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “...randomisation was done using computer generated series of numbers...”
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not reported

Rapone 2021 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low number of dropouts in both groups (Gp A 4, Gp B 3)
Selective reporting (reporting bias)	High risk	Data not reported in full for any outcome
Other bias	Low risk	None apparent

Rodrigues 2015

Study characteristics	
Methods	**Trial design:** 2-arm RCT **Location:** University Hospital Pedro Ernesto/UERJ, Brazil **Setting:** hospital **Number of centres:** 1 **Recruitment period:** not reported **Funding source:** none declared
Participants	**Inclusion criteria:** diagnosis of T2DM (WHO) for, at least 1 yr; severe chronic periodontitis (International Workshop for Classification of Periodontal Disease) - at least 2 sites with PD ≥ 6 mm and 2 sites with CAL ≥ 5 mm; minimum age of 35 yrs; 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 mths **Age at baseline (yrs):** Gp A 59.4 (SD 8.4), Gp B 55.8 (SD 8.4) (P = NS) **Sex (M:F):** 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 (SD 4.8), Gp B 16.8 (SD 7.3) **Metabolic control:** HbA1c % Gp A 10.9 (SD 13.3), Gp B 8.2% (SD 3.0) **Other clinical investigations:** periodontal clinical examination **Number randomised:** 26 **Number evaluated:** 26 at 3 mths (13/13)
Interventions	**Comparison: SRP vs usual care** Gp A (n = 13): 4 to 6 sessions of SRP Gp B (n = 13): biofilm control and advice on oral hygiene **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HbA1c

Rodrigues 2015 *(Continued)*

	Secondary: serum osteocalcin level, clinical periodontal parameters (PD, CAL, BOP, PI), glycaemic level (glycose, estimated glycaemia), lipidic profile (total cholesterol, HDL-C, LDL-C, 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "The 26 initially selectioned patients were randomly divided into group test and control" – no description
Allocation concealment (selection bias)	Unclear risk	No description
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	High risk	Quote: "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" – clinical operators were the outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout or participant loss registered
Selective reporting (reporting bias)	Low risk	All outcome data reported for both groups
Other bias	Unclear risk	Skin colour, educational level, marital status, family history of diabetes data unreported

Singh 2008

Study characteristics

Methods	**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:** "Source of support: Nil"
Participants	**Inclusion criteria:** ≥ 30 yrs old, either sex; T2DM; moderate to advanced periodontitis (30% or > of examined teeth with ≥ 4 mm PD); 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 mths; antibiotic administration in prior 3 mths; < 16 remaining natural teeth

Singh 2008 *(Continued)*

	Age at baseline: not reported **Sex (M:F):** not reported **Tobacco use:** not reported **Alcohol consumption:** not reported **Diabetes type:** T2DM **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, postprandial blood glucose (PPBG) **Number randomised:** 45 **Number evaluated:** 45
Interventions	**Comparison: SRP + OHI vs SRP + OHI + doxycycline vs 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 per day 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 participants received extractions, or whether this may have affected treatment outcomes **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HbA1c (at baseline and 3 mths) **Secondary:** PI, GI, PPD, CAL (at baseline and 3 mths)
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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "They were randomly divided into three groups of 15 patients each" - no further details

Singh 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants reported as lost to follow-up. Analysis assumed to have been ITT though not specifically reported
Selective reporting (reporting bias)	Unclear risk	Planned outcomes reported for 3 mths; however, assessed at 1 mth 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 risk	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

Study characteristics	
Methods	**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:** diagnosed with T2DM at least 1 yr prior to study; moderately poor glycaemic control (HbA1c between 7.5% and 9.5%); aged 70 years; BMI 19-26 kg/m^2 in women, BMI 20-27 kg/m^2 in men; no medication changes during the 3 mths 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 over 4 mm, or > 60% teeth with PD > 4 mm and attachment loss > 3 mm; no periodontal treatment in the previous 6 mths; no antibiotics or NSAIDS administered in previous 3 mths; no serious systemic diseases or complications **Exclusion criteria:** systemic inflammatory diseases (rheumatoid arthritis, etc), blood disease, liver damage, kidney disease or trauma **Age at baseline (yrs):** Gp A mean 55.13 (SD 11.16); Gp B mean 54.23 (SD 10.85) **Sex (M:F):** overall: 67:90, Gp A: 35:47, Gp B: 32:43

Sun 2011 *(Continued)*

	Tobacco use: smokers excluded **Alcohol consumption:** not reported **Diabetes type:** all T2DM **Duration since diabetes diagnosis:** > 1 yr **Metabolic control:** mean HbA1c % at baseline Gp A: 8.75% (SD 0.67), Gp B: 8.70% (SD 0.65) **Antidiabetic therapy:** not reported; study inclusion requirement was no medication changes during study period **Other medical conditions:** none **Other clinical investigations:** sulcus bleeding index; FPG; triglycerides; total cholesterol; HDL-C; LDL-C; FINS, fasting insulin; homeostasis model assessment of insulin resistance; hs-CRP; TNF; interleukin-6; adiponectin **Number randomised:** 190 **Number evaluated:** 157
Interventions	**Comparison: SRP + OHI + antibiotics vs no intervention** Gp A (n = 82 after removal of people 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 people not completing the study): no periodontal treatment (no indication if OHI delivered) **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HbA1c at baseline and 3 mths **Secondary:** PD, CAL, BI, and PI at baseline and 3 mths
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 Not detailed anywhere how many were originally in each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "...patients were randomly divided into two Groups." This is the only information reported. The study is not explicitly described as being an RCT
Allocation concealment (selection bias)	Unclear risk	Not reported

Sun 2011 *(Continued)*

Blinding of participants	High risk	Quote: "study was not blinded"
Blinding of clinical operator	High risk	Quote: "study was not blinded"
Blinding of periodontal outcome assessor	High risk	Quote: "study was not blinded"
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol analysis: not all participants analysed in groups randomised to, regardless of intervention actually received. All losses accounted for by rationale, but not by study arm: "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)"
Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Low risk	No other apparent biases

Telgi 2013

Study characteristics	
Methods	**Trial design:** 3-arm, parallel RCT **Location:** Diabetic Centre, Moradabad, India **Setting:** hospital ("dental clinic wing of the Diabetic Centre") **Number of centres:** 1 **Recruitment period:** unknown **Funding source:** none mentioned
Participants	**Inclusion criteria:** with T2DM, blood sugar controlled only with oral hypoglycaemic agents, mild to moderate periodontitis (PD of 4-5 mm), presence of a minimum of 28 teeth, no systemic antibiotic administration, no periodontal treatment in last 6 mths **Exclusion criteria:** with systemic diseases other than T2DM, tobacco and alcohol users, and suffering from oral disease and needing emergency treatment **Age at baseline (yrs):** 35 to 45 **Sex (M:F):** not reported **Tobacco use:** no - exclusion criteria **Alcohol consumption:** no - exclusion criteria **Diabetes type:** T2DM **Duration since diabetes diagnosis:** not reported **Metabolic control:** mean HbA1c % Gp A 7.68 (SD 0.63), Gp B 7.56 (SD 0.59), Gp C 7.74 (SD 0.59) **Other clinical investigations:** fasting blood sugar

Telgi 2013 *(Continued)*

	Number randomised: 60 (20 per gp) **Number evaluated:** 60
Interventions	**Comparison: SRP and chlorhexidine mouthwash vs OHI and chlorhexidine mouthwash vs OHI** Gp A: scaling, mouthwash, and brushing (patients, who had undergone scaling, advised to regularly use 0.12% mouthwash (once daily) and brush (twice daily)) Gp B: mouthwash and brushing (patients advised to regularly use 0.12% chlorhexidine mouthwash (once daily) and brush (twice daily)) Gp C: brushing only (patients advised to brush twice daily) **Duration of follow-up:** 3 mths
Outcomes	HbA1c, fasting blood sugar, PPD, GI, PI, relevant drug history Measured at baseline and after 3 mths of intervention
Notes	**Sample size calculation:** based on a pilot study, a sample size of 15 patients in each group was estimated considering (α = 0.05 (95% CI) and β=0.2 (80% power)). The mean difference between the glycated haemoglobin (HbA1c) levels of the untreated group and treated group was observed to be 1.08 ± 0.93. For a 5% type I error and 20% type II error, and it was found to be 15 subjects. Due to the longitudinal nature of the study, anticipating the attrition of some participants, a sample size of 20 patients in each group was recruited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided equally among 3 groups"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	High risk	Not feasible
Blinding of clinical operator	High risk	Not feasible
Blinding of periodontal outcome assessor	Low risk	Quote: "examiner blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Tsobgny-Tsague 2018

Study characteristics

Tsobgny-Tsague 2018 *(Continued)*

Methods	**Trial design:** 2-arm RCT **Location:** Yaounde Central Hospital, Cameroon **Setting:** hospital **Number of centres:** 1 **Recruitment period:** December 2014 to May 2015 (5 mths) **Funding source:** none
Participants	**Inclusion criteria:** poorly controlled T2DM, moderate to severe chronic periodontitis according to the 2012 CDC-AAP classification and having at least 11 teeth **Exclusion criteria:** periodontal treatment (SRP) or experimented any alteration of the diabetes treatment 6 mths 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 (yrs):** Gp A 51.2 (SD 7.8), Gp B 51.7 (SD 9.9) **Sex (M:F):** Gp A 8:7, Gp B 5:10 **Tobacco use:** not admitted to the study **Alcohol consumption:** not admitted to the study **Diabetes type:** T2DM (poorly controlled) **Duration since diabetes diagnosis:** Gp A 5.0 ± 3.86, Gp B 4.26 ± 0.825 converted from mths to yrs **Metabolic control:** HbA1c % Gp A 9.7 (SD 1.6), Gp B 8.9 (SD 0.9) **Other clinical investigations:** none **Number randomised:** 34 **Number evaluated:** 30 at 3 mths (evaluations also at 6 wks)
Interventions	**Comparison: full mouth SRP/OHI followed by a subgingival irrigation with a 10% povidone iodine solution vs no treatment (time-weighted)** Gp A (n = 15): all participants of the treatment group received dental floss and chlorhexidine gluconate 0.2% as mouthwash (10 ml twice daily for 5 days). All participants were instructed in oral hygiene methods: using of the modified Bass technique for toothbrushing, and using of soft bristled toothbrush Gp B (n = 15) **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HbA1c **Secondary:** O'Leary plaque index, Aainamo and Bay gingival bleeding index, PD, and 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

Tsobgny-Tsague 2018 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Block randomisation Quote: "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 risk	Drawn from a bag with 6 blocks. Researchers were then however aware of which block was allocated to each group
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	Quote: "The periodontal examiners were masked to participants' assignment"
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 lost to follow-up in each group, reasons provided
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Low risk	None apparent

Vergnes 2018

Study characteristics	
Methods	**Trial design:** RCT **Location:** diabetology departments in South-Western France (Toulouse-Rangueil and Bordeaux Haut-Leveque) **Number of centres:** 2 **Recruitment period:** 54 mths (February 2010 to 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 1 yr duration. HbA1c between 7.0% and 9.5% uncontrolled. Unchanged treatment regimen for 3/12 ≥ 6 permanent natural teeth. A diagnosis of periodontal disease with at least 4 teeth standing and with at least 1 probed site with PPD ≥ 4 mm and CAL ≥ 3 mm **Exclusion criteria:** none stated **T1DM participants** Gp A n = 32, Gp B n = 35

Vergnes 2018 *(Continued)*

	Age at baseline (yrs): Gp A 50.9 (SD 9.4), Gp B 53.7 (SD 13.8) **Sex (M:F):** Gp A 19:13, Gp B 20:15 **Tobacco use:** GP A 7, Gp B 8 **Alcohol consumption:** no record **Duration since diabetes diagnosis (yrs):** Gp A 25.0 (SD 11.0), Gp B 25.2 (SD 13.9) **Metabolic control:** HbA1c % Gp A 7.84 (SD 0.65), Gp B 7.83 (SD 0.64) **T2DM participants** Gp A n = 13, Gp B n = 11 **Age:** Gp A 68.3 (SD 9.3), Gp B 63.1 (SD 4.0) **Sex (M:F):** Gp A 5:8, Gp B 2:9 **Tobacco use:** GP A 2, Gp B 0 **Alcohol consumption:** no record **Duration since diabetes diagnosis (yrs):** Gp A 18.1 (SD 11.2), Gp B 19.9 (SD 13.0) **Metabolic control:** HbA1c % Gp A 7.96 (SD 0.84), Gp B 7.78 (SD 0.52) **Other clinical investigations:** fructosamine, weight (kg), quality of life **Number randomised:** 91 (T1DM = 67, T2DM = 24) **Number evaluated:** 88 at 3 mths (T1DM = 65, T2DM = 23)
Interventions	**Comparison: SRP + antibiotics vs delayed treatment** Gp A (immediate treatment): non-surgical SRP, systemic antibiotics (amoxicillin 2 g/day for 7 days), scaling carried out over 10 days, OHI, subgingival chlorhexidine Gp B (delayed treatment): then same intervention as above Separate analysis type 1 and type 2 DM **Duration of follow-up:** 3 mths
Outcomes	**Primary:** HBA1c **Secondary:** PPD, CAL, BOP (also recession, periodontal epithelial surface area PESA (mm), periodontal inflamed surface area)
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% dropout rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants	High risk	Not possible

Vergnes 2018 *(Continued)*

Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	High risk	Not possible due to time weighting for periodontal parameters
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were presented and analysed on ITT basis
Selective reporting (reporting bias)	Low risk	Data separately presented as type 1, type 2 and combined
Other bias	Unclear risk	Trial was stopped early with only 91 recruited. Per-protocol analysis excluded participants who reported not toothbrushing twice a day

Wang S 2017

Study characteristics	
Methods	**Trial design:** parallel-group, 2-arm RCT **Location:** Xiamen Dentistry Hospital, China **Setting:** hospital **Number of centres:** 1 **Recruitment period:** June 2014 to December 2014 (6 mths) **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 yr, HbA1c between 6.5% to 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 mths, antibiotic or NSAID past 3 mths, serious systemic diseases/complications **Age at baseline (yrs):** Gp A 61.58 (SD 4.69), Gp B 61.9 (SD 6.75) **Sex (M:F):** Gp A 12:7, Gp B 14:6 **Tobacco use:** 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:** T2DM **Duration since diabetes diagnosis (yrs):** Gp A 8.5 (SD 3.1), Gp B 7.7 (SD 4.7) **Metabolic control:** HbA1c % Gp A 7.63 (SD 0.89), Gp B 7.70 (SD 1.32) **Other clinical investigations:** TNF-a, IL-6, adiponectin, FGF21 **Number randomised:** 44 **Number evaluated:** at 3 mths Gp A = 19, Gp B = 20

Wang S 2017 *(Continued)*

Interventions	**Comparison: SRP vs no treatment** 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 mths
Outcomes	**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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	44 random numbers generated using computer programme SPSS version 17.0
Allocation concealment (selection bias)	Low risk	Quote: “These numbers were used to recruit and blindly randomize 44 subjects.” Assumed adequate
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	High risk	Quotes: "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 risk	Low dropout rates (3 in intervention group and 2 in control) and reasons provided, although per-protocol analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported in full (per-protocol)
Other bias	Low risk	None apparent

Wang Y 2017

Study characteristics

Methods	**Trial design:** 2-arm RCT **Location:** Department of Medicine, Queen Mary Hospital, Hong Kong **Setting:** hospital

Wang Y 2017 *(Continued)*

	Number of centres: 1, but periodontal screening in Prince Philip Dental Hospital (PPDH) **Recruitment period**: June 2015 to August 2016 **Funding source:** none **Aim:** to investigate the effects of periodontal treatment on immuno-inflammatory gene expression of endothelial progenitor cells in diabetic patients
Participants	**Inclusion criteria:** clinical diagnosis of DM for at least 5 yrs with HbA1c level more than 6.5%; consistent antidiabetic treatment 3 mths prior to the study; and at least 40 yrs old Moderate to severe chronic periodontitis criteria (Li 2009) were met, including more than 6 sites with PD ≥ 4 mm and over 25% of sites with interproximal clinical attachment loss ≥ 5 mm as well as at least 10 teeth present **Exclusion criteria:** history of cardiovascular disease, people with antibiotic/anti-inflammatory treatment within 3 mths prior to the study or those requiring antibiotic prophylaxis **Age at baseline (yrs):** Gp A 65 (SD 8), Gp B 68 (SD 3) **Sex (M:F):** Gp A 6:5, Gp B 3:4 **Tobacco use:** Gp A 1, Gp B 1 **Alcohol consumption:** not recorded **Diabetes type:** T2DM **Duration since diabetes diagnosis (yrs):** Gp A 19 (SD 6), Gp B 18 (SD 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:** 18 at 6 mths
Interventions	**Comparison: OHI, extraction, scaling and root surface debridement (hand and ultrasonic) vs delayed treatment** Reviewed every 4 to 6 wks Gp A (n = 11) Gp B (n = 7) **Duration of follow-up:** 6 mths 1 loss to follow-up (control group)
Outcomes	**Primary:** HbA1c (main outcomes 9 inflammatory mediators like IL-6 and IL-8) **Secondary:** CAL, PD, BOP, and PI Peripheral blood samples taken to analyse endothelial progenitor cells at baseline and 6 mths after treatment
Notes	**Sample size calculation:** none
Risk of bias	

Bias	Authors' judgement	Support for judgement

Wang Y 2017 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	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 risk	Generated by primary investigator
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	Both periodontal and medical tests were conducted as blinded. Periodontal assessor calibrated for intra-examiner reproducibility
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 dropout. All accounted for in analysis
Selective reporting (reporting bias)	Low risk	HbA1c was not the main focus of the study
Other bias	Low risk	None apparent

Yun 2007

Study characteristics	
Methods	**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 T2DM and no history of another major illness, no antibiotics or other medications received for at least 3 previous mths; at least 14 standing teeth, PPD 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 mths prior to baseline examination **Exclusion criteria:** pregnancy or lactation **Age at baseline (yrs):** Gp A mean 53.41 (SD 2.42), Gp B mean 55.10 (SD 2.64) **Sex (M:F):** overall: 22:24, Gp A: 10:13, Gp B: 12:11 **Tobacco use:** not reported **Alcohol consumption:** not reported **Diabetes type:** T2DM **Duration since diabetes diagnosis:** "newly diagnosed"

Yun 2007 *(Continued)*

	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 - "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 vs doxycycline alone** Gp A (n = 23): participants were treated with 5 x 1-hr 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 wks last session (3 mths 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 mths
Outcomes	**Primary:** HbA1c (at baseline and 4 mths) **Secondary:** BOP, PPD, CAL, PI (at baseline and 4 mths)
Notes	**Sample size calculation:** not 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly divided"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not reported, but there do not seem to be any dropouts. ITT analysis

Yun 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	All planned outcomes reported
Other bias	Unclear risk	Poorly reported

Zhang 2013

Study characteristics	
Methods	**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 T2DM for more than 1 yr. A diagnosis of T2DM should have met at least 1 of the following criteria: PPG 200 mg/dL (11.1 mmol/L); FPG 126 mg/dL (7.0 mmol/L); 2-hr oral glucose tolerance test 200 mg/dL (11.1 mmol/L). In addition, participants should have had the following attributes: be 35 to 80 yrs 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 mths before recruitment of at least 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 mths; underwent modified diabetes treatment strategy within 3 mths; had periodontal treatment within the past 12 mths; 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 (yrs):** Gp A mean 60.4 (SD 9.77); Gp B mean 62.7 (SD 10.7) (P = 0.377) **Sex (M:F):** overall: 31:40, Gp A: 21:28, Gp B: 10:12 (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:** T2DM **Duration since diabetes diagnosis (yrs):** Gp A 8.63 (SD 4.20); Gp B 7.29 (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 combination Overall: 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

Zhang 2013 *(Continued)*

	Number evaluated: 72 at 3 mths, 71 at 6 mths
Interventions	**Comparison: SRP + OHI vs delayed treatment** Gp A (n = 50): SRP (supra/subgingival scaling (Cavitron Bobcat Pro, Dentsply, USA); manual curettage (Hu-Friedy, USA)) + OHI (within 2 wks of baseline examination) Gp B (n = 25): delayed treatment Gp A subdivided at 3 mths into Gp C (n = 25; SRP + OHI + "sub-enhanced root planing" ("sub-ERP")) and Gp D (n = 25; SRP + OHI + "subprophylaxis") - HbA1c not reported with this further breakdown **Duration of follow-up:** 6 mths
Outcomes	**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 participants per group SRP vs 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

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Pre-prepared randomisation in group A, B, and C. No description of sequence generation
Allocation concealment (selection bias)	Low risk	Number-coded envelopes Quote: "Cards with group identification were prepared and placed in number-coded envelopes as defined by SPSS (version 17.0; IBM, New York, NY, USA)"
Blinding of participants	High risk	Not possible
Blinding of clinical operator	High risk	Not possible
Blinding of periodontal outcome assessor	Low risk	Blinded examiner Quote: "The single blind method was used in this study as the examiner was blind to the intervention for the patients"
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 lost to follow-up: Gp A: 1 lost at evaluation 2 (3 mths); Gp B: 2 lost at evaluation 2 (3 mths), and 1 at evaluation 3 (6 mths). Reasons provided Per-protocol analysis
Selective reporting (reporting bias)	High risk	HbA1c data presented inconsistently; periodontal outcomes presented as graphs without data. Email to authors bounced

Zhang 2013 *(Continued)*

Other bias	Low risk	No other apparent biases

AAP: American Academy of Periodontology; aPDT: antimicrobial photodynamic therapy; AL: attachment level; BI: bleeding index; bid: twice daily; BMI: body mass index; BOP: bleeding on probing; CAL: clinical attachment level; CDC: US Centers for Disease Control and Prevention; CHX: chlorhexidine; CI: confidence interval; DM: diabetes mellitus; F: female; FGF21: fibroblast growth factor 21; FMD: full mouth disinfection; FPG: fasting plasma glucose; GBI: gingival bleeding index; GI: gingival index; gp: group; GR: gingival recession; h: hours; hs-CRP: high-sensitivity C-reactive protein; HbA1c: glycated haemoglobin; HDL-C: high density lipoprotein cholesterol; ITT: intention-to-treat; LDL-C: low density lipoprotein cholesterol; M: male; mg: milligram; ml: millilitre; min: minute; mm: millimetres; mths: months; NS: non-significant; NSAIDS: non-steroidal anti-inflammatory drugs; OAD: oral antidiabetics; OHI: oral hygiene instruction; PD: probing depth; PI: plaque index; po: orally; PPD: probing pocket depth; PPG: postprandial plasma glucose; qid: 4 times a day; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SES: socioeconomic status; SRP: scaling and root planing; TC: total cholesterol; TNF: tumor necrosis factor; T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; VPI: visible plaque index; vs: versus; wks: weeks; WHO: World Health Organization; yrs: years.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albrecht 1988	No HbA1c outcome reported. Study was not translated to English but advice sought from a Hungarian speaker on the content
Botero 2013	Poorly reported. Further data needed (particularly accurate HbA1c means/standard deviations, data re: statin use) from study author to complete assessment. Attempts to contact authors unsuccessful. Categorised as 'awaiting classification' in 2015 version of review
Chee 2006	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	Observational study
Elsadek 2020	No mention of randomisation
Goel 2017	Quasi-randomised study
Khader 2010	Use of a non-periodontal intervention: full-mouth tooth extraction for patients whose remaining teeth were deemed to be in a hopeless condition and indicated for extraction
Mammen 2017	Does not mention randomisation
NCT01255254	Correspondence with trial investigator (May 2013) indicated trial was abandoned due to recruitment issues
Peña Sisto 2018	Quasi-randomised study
Phetnin 2020	Ineligible design - 2 health centres, 1 randomised to each intervention

HbA1c = glycated haemoglobin.

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12605000260628

Study name	Assessment of diabetes after periodontal treatment

ACTRN12605000260628 *(Continued)*

	Trial acronym: ADAPT
Methods	Blinded RCT, with computer-generated random sequence generation into equal sized groups, with allocation concealed by use of sealed opaque envelopes
Participants	Aiming for 60 participants **Inclusion criteria:** either sex; at least 35 years old; able to give informed consent; random glucose > 200 mg/dL; at least 16 teeth; chronic periodontitis **Exclusion criteria:** pregnancy; gross dental caries; requirement for antibiotic cover for dental treatment; anticoagulant therapy; other serious illness
Interventions	**Comparison: SRP + antimicrobial toothpaste (triclosan) vs delayed treatment + placebo toothpaste** Gp A: "periodontal treatment" + triclosan/fluoride toothpaste Gp B: triclosan/fluoride toothpaste + delayed "periodontal treatment" **Duration of follow-up:** 12 months
Outcomes	**Primary:** HbA1c, C-peptide, measured at 6 and 12 months **Secondary:** unspecified - "response to periodontal treatment" (assume periodontal parameters), measured at 2 weeks, 6 months, and 12 months; inflammatory markers, plaque bacteria & antibodies also assessed - time points not specified
Starting date	"Anticipated" to be 1 September 2005
Contact information	Michelle Robbins/Mary Cullinan: m.cullinan@uq.edu.au
Notes	Retrospectively registered Funding source: Australian Dental Research Fund and Colgate Palmolive Co USA Dr Cullinan confirmed (February 2015), completed but not published. Not able to share results (unknown if analysed)

NCT01291875

Study name	Periodontal treatment and metabolic control in type 2 diabetic patients
Methods	2-arm RCT
Participants	120 participants **Inclusion criteria:** over 30 years old; diagnosed with T2DM; consenting to the study; with signs of severe periodontitis (at least 50 periodontal pockets, PPD > 4 mm and BOP) **Exclusion criteria:** pregnancy/lactation; 'chronic treatment' of 2 weeks or more with specific medications known to affect periodontal status (phenytoin or cyclosporine) within 1 month of baseline visit; known HIV or hepatitis (B, C); uncontrolled systemic diseases (cardiovascular diseases including hypertension, liver, pulmonary diseases, end stage renal failure) and/or neoplasm; not capable of providing informed consent; chronic antibiotic therapy or who require antibiotic coverage for periodontal procedures
Interventions	**Comparison: SRP vs mechanical debridement**

NCT01291875 *(Continued)*

	Gp A: SRP under local analgesia (depending on the severity in 1 session or 2 sessions within 2 days) + extraction of indicated hopeless teeth + additional SRP where necessary at follow-up Gp B: "supragingival biofilm control": supragingival mechanical instrumentation/polishing using hand and machine driven (piezoelectric) instrumentation **Duration of follow-up:** 12 months
Outcomes	Changes in HbA1c and serum inflammatory markers of inflammation after periodontal intervention Outcomes measured at 2, 6, and 12 months
Starting date	February 2011
Contact information	Hilana Artese: hilanartese@gmail.com; Giuseppe Romito: garomito@usp.br
Notes	Emailed Drs Artese and Romito to check if trial completed/obtain unpublished results, but no response

NCT01901926

Study name	Periodontal treatment and glycaemic control
Methods	RCT
Participants	184 T2DM patients with mild-moderate periodontitis
Interventions	**Comparison: SRP vs no treatment** Gp A: SRP Gp B: no treatment **Duration of follow-up:** 9 months
Outcomes	**Primary:** HbA1c (at 3, 6, and 9 months) **Secondary:** BOP, CAL, PPD (at 3, 6, and 9 months) Outcomes measured at 9 months
Starting date	December 2012
Contact information	Salman Aziz: dr_salman_aziz@yahoo.com
Notes	Emailed Dr Aziz to check if trial completed/obtain unpublished results, but no response

U1111-1124-3635

Study name	Influence of periodontal treatment in periodontitis and diabetes control
Methods	3-arm RCT **Follow-up duration:** 6 months

U1111-1124-3635 *(Continued)*

Participants	150 T2DM patients with chronic periodontitis
Interventions	**Comparison: SRP vs ultrasonic debridement vs OHI** Gp A: SRP Gp B: ultrasonic debridement Gp C: OHI
Outcomes	Primary: HbA1c Secondary: PI, PPD Outcomes measured at 6 months
Starting date	August 2011
Contact information	Renata Cimões: renata.cimoes@globo.com
Notes	Emailed to check if completed/unpublished results available: no response

BOP = bleeding on probing; CAL = clinical attachment level; Gp = group; HbA1c = glycated haemoglobin; OHI = oral hygiene instruction; PI = plaque index; PPD = probing pocket depth; RCT = randomised controlled trial; SRP = scaling and root planing; T2DM = type 2 diabetes mellitus.

DATA AND ANALYSES

Comparison 1. Periodontal treatment versus no active intervention/usual care

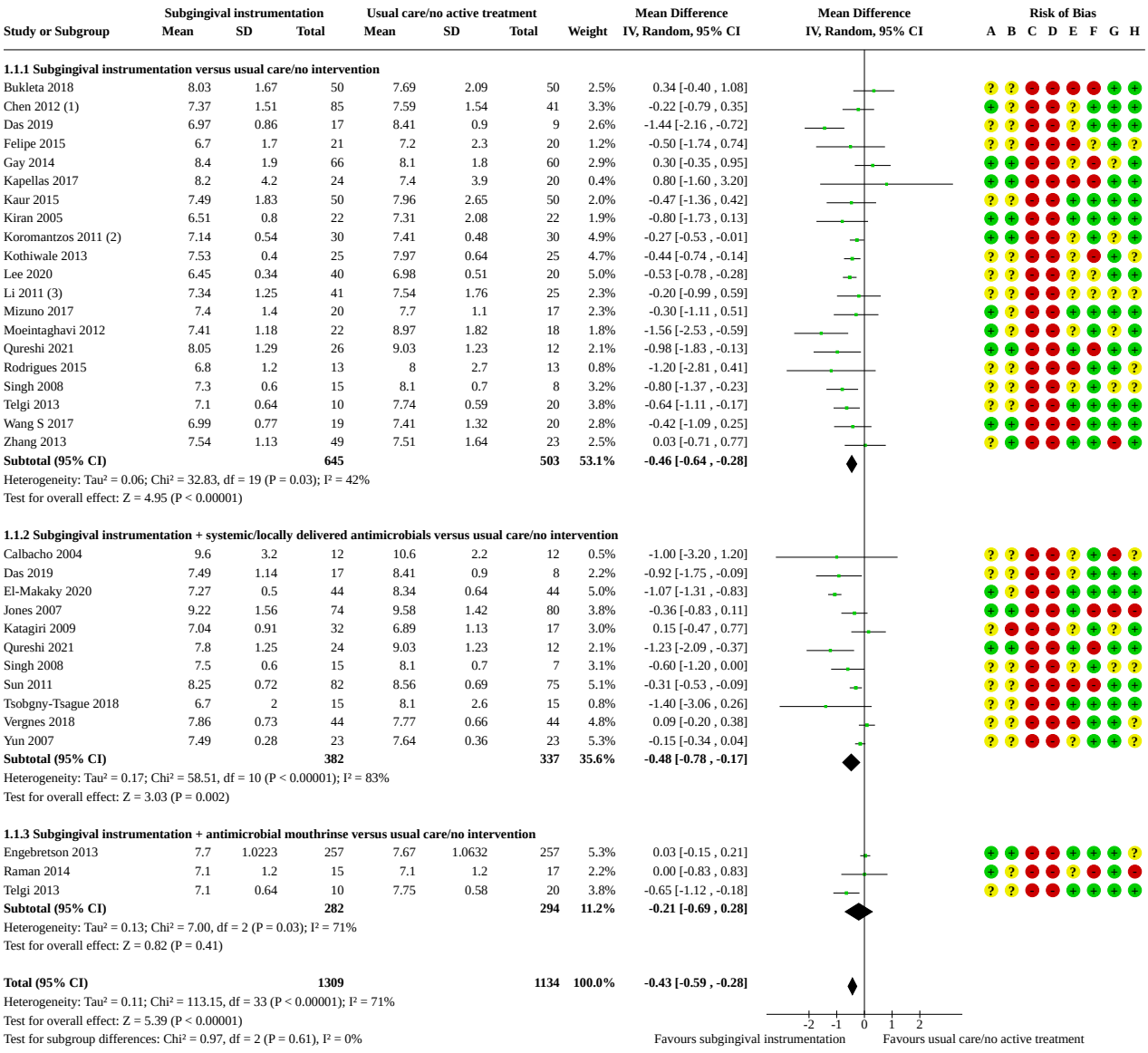
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 HbA1c at 3-4 months	30	2443	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.59, -0.28]
1.1.1 Subgingival instrumentation versus usual care/no intervention	20	1148	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.64, -0.28]
1.1.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	11	719	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.78, -0.17]
1.1.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	3	576	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.69, 0.28]
1.2 HbA1c at 6 months	12	1457	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.52, -0.08]
1.2.1 Subgingival instrumentation versus usual care/no intervention	10	858	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.59, -0.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	2	85	Mean Difference (IV, Random, 95% CI)	-0.96 [-3.24, 1.32]
1.2.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	1	514	Mean Difference (IV, Random, 95% CI)	0.00 [-0.22, 0.22]
1.3 HbA1c at 12 months	1	264	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.55, -0.45]
1.3.1 Subgingival instrumentation versus usual care/ no intervention	1	264	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.55, -0.45]
1.4 CAL at 3-4 months	18	1606	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.65, -0.31]
1.4.1 Subgingival instrumentation versus usual care/no intervention	11	631	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.67, -0.24]
1.4.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	8	483	Mean Difference (IV, Random, 95% CI)	-0.63 [-0.97, -0.28]
1.4.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	2	492	Mean Difference (IV, Random, 95% CI)	-0.13 [-0.42, 0.17]
1.5 CAL at 6 months	5	789	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.77, -0.26]
1.5.1 Subgingival instrumentation versus usual care/no intervention	4	329	Mean Difference (IV, Random, 95% CI)	-0.66 [-0.80, -0.53]
1.5.2 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	1	460	Mean Difference (IV, Random, 95% CI)	-0.25 [-0.36, -0.14]
1.6 PPD at 3-4 months	21	1755	Mean Difference (IV, Random, 95% CI)	-0.56 [-0.72, -0.40]
1.6.1 Subgingival instrumentation versus usual care/no intervention	12	691	Mean Difference (IV, Random, 95% CI)	-0.48 [-0.70, -0.26]
1.6.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	9	532	Mean Difference (IV, Random, 95% CI)	-0.76 [-1.09, -0.43]
1.6.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	3	532	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.41, -0.20]
1.7 PPD at 6 months	8	1181	Mean Difference (IV, Random, 95% CI)	-0.50 [-0.70, -0.29]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.1 Subgingival instrumentation versus usual care/no intervention	6	672	Mean Difference (IV, Random, 95% CI)	-0.56 [-0.81, -0.30]
1.7.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	1	49	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.78, -0.02]
1.7.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	1	460	Mean Difference (IV, Random, 95% CI)	-0.28 [-0.37, -0.19]
1.8 PPD at 12 months	1	264	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.18, -0.62]
1.8.1 Subgingival instrumentation versus usual care/no intervention	1	264	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.18, -0.62]
1.9 BOP at 3-4 months	14	1324	Mean Difference (IV, Random, 95% CI)	-15.56 [-21.77, -9.36]
1.9.1 Subgingival instrumentation versus usual care/no intervention	9	566	Mean Difference (IV, Random, 95% CI)	-15.38 [-24.98, -5.78]
1.9.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	5	298	Mean Difference (IV, Random, 95% CI)	-15.93 [-26.09, -5.77]
1.9.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	1	460	Mean Difference (IV, Random, 95% CI)	-14.60 [-19.17, -10.03]
1.10 BOP at 6 months	7	862	Mean Difference (IV, Random, 95% CI)	-21.57 [-33.18, -9.96]
1.10.1 Subgingival instrumentation versus usual care/no intervention	5	340	Mean Difference (IV, Random, 95% CI)	-27.27 [-42.09, -12.45]
1.10.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	1	49	Mean Difference (IV, Random, 95% CI)	-6.80 [-16.27, 2.67]
1.10.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	1	473	Mean Difference (IV, Random, 95% CI)	-11.80 [-16.30, -7.30]
1.11 PI at 3-4 months	18	1521	Std. Mean Difference (IV, Random, 95% CI)	-2.05 [-2.57, -1.53]
1.11.1 Subgingival instrumentation versus usual care/no intervention	11	621	Std. Mean Difference (IV, Random, 95% CI)	-1.79 [-2.57, -1.00]
1.11.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	6	368	Std. Mean Difference (IV, Random, 95% CI)	-2.46 [-3.28, -1.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	3	532	Std. Mean Difference (IV, Random, 95% CI)	-4.15 [-6.78, -1.51]
1.12 PI at 6 months	8	1149	Std. Mean Difference (IV, Random, 95% CI)	-1.48 [-2.14, -0.83]
1.12.1 Subgingival instrumentation versus usual care/no intervention	7	689	Std. Mean Difference (IV, Random, 95% CI)	-1.69 [-2.55, -0.83]
1.12.2 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	1	460	Std. Mean Difference (IV, Random, 95% CI)	-0.46 [-0.65, -0.28]
1.13 PI at 12 months	1	264	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.16, -0.66]
1.13.1 Subgingival instrumentation versus usual care/no intervention	1	264	Std. Mean Difference (IV, Random, 95% CI)	-0.91 [-1.16, -0.66]
1.14 GI at 3-4 months	12	1109	Std. Mean Difference (IV, Random, 95% CI)	-1.75 [-2.27, -1.24]
1.14.1 Subgingival instrumentation versus usual care/no intervention	7	343	Std. Mean Difference (IV, Random, 95% CI)	-1.91 [-2.83, -0.98]
1.14.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention	4	234	Std. Mean Difference (IV, Random, 95% CI)	-2.52 [-3.43, -1.61]
1.14.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	3	532	Std. Mean Difference (IV, Random, 95% CI)	-0.73 [-0.90, -0.55]
1.15 GI at 6 months	6	1083	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.29, -0.56]
1.15.1 Subgingival instrumentation versus usual care/no intervention	5	569	Std. Mean Difference (IV, Random, 95% CI)	-1.05 [-1.25, -0.86]
1.15.2 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention	1	514	Std. Mean Difference (IV, Random, 95% CI)	-0.47 [-0.64, -0.29]
1.16 GI at 12 months	1	264	Std. Mean Difference (IV, Random, 95% CI)	-1.13 [-1.39, -0.87]
1.16.1 Subgingival instrumentation versus usual care/no intervention	1	264	Std. Mean Difference (IV, Random, 95% CI)	-1.13 [-1.39, -0.87]

Analysis 1.1. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 1: HbA1c at 3-4 months



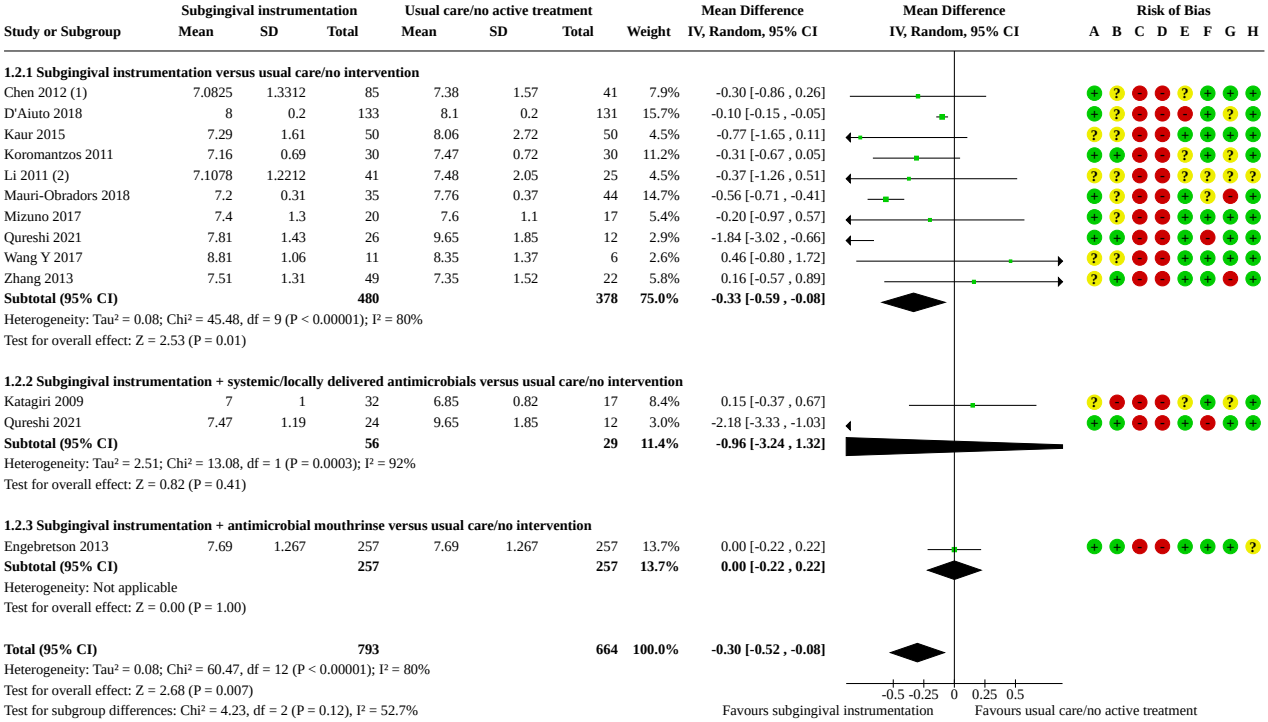
Footnotes

(1) SGI + additional mechanical therapy
(2) SGI + OHI vs mechanical therapy (supragingival cleaning) + OHI
(3) Periodontal treatment described as "mechanical therapy"

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants
(D) Blinding of clinical operator
(E) Blinding of periodontal outcome assessor
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.2. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 2: HbA1c at 6 months

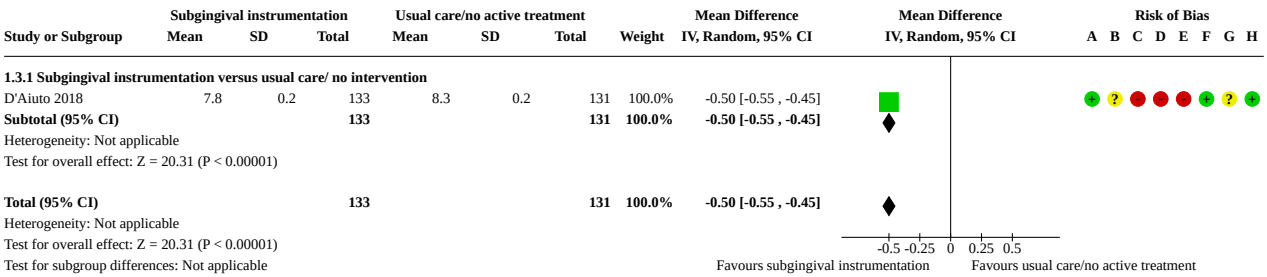


Study or Subgroup	Subgingival instrumentation Mean	SD	Total	Usual care/no active treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Subgingival instrumentation versus usual care/no intervention								
Chen 2012 (1)	7.0825	1.3312	85	7.38	1.57	41	7.9%	-0.30 [-0.86 , 0.26]
D'Aiuto 2018	8	0.2	133	8.1	0.2	131	15.7%	-0.10 [-0.15 , -0.05]
Kaur 2015	7.29	1.61	50	8.06	2.72	50	4.5%	-0.77 [-1.65 , 0.11]
Koromantzos 2011	7.16	0.69	30	7.47	0.72	30	11.2%	-0.31 [-0.67 , 0.05]
Li 2011 (2)	7.1078	1.2212	41	7.48	2.05	25	4.5%	-0.37 [-1.26 , 0.51]
Mauri-Obradors 2018	7.2	0.31	35	7.76	0.37	44	14.7%	-0.56 [-0.71 , -0.41]
Mizuno 2017	7.4	1.3	20	7.6	1.1	17	5.4%	-0.20 [-0.97 , 0.57]
Qureshi 2021	7.81	1.43	26	9.65	1.85	12	2.9%	-1.84 [-3.02 , -0.66]
Wang Y 2017	8.81	1.06	11	8.35	1.37	6	2.6%	0.46 [-0.80 , 1.72]
Zhang 2013	7.51	1.31	49	7.35	1.52	22	5.8%	0.16 [-0.57 , 0.89]
Subtotal (95% CI)			**480**			**378**	**75.0%**	**-0.33 [-0.59 , -0.08]**
Heterogeneity: Tau² = 0.08; Chi² = 45.48, df = 9 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 2.53 (P = 0.01)								
1.2.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention								
Katagiri 2009	7	1	32	6.85	0.82	17	8.4%	0.15 [-0.37 , 0.67]
Qureshi 2021	7.47	1.19	24	9.65	1.85	12	3.0%	-2.18 [-3.33 , -1.03]
Subtotal (95% CI)			**56**			**29**	**11.4%**	**-0.96 [-3.24 , 1.32]**
Heterogeneity: Tau² = 2.51; Chi² = 13.08, df = 1 (P = 0.0003); I² = 92%								
Test for overall effect: Z = 0.82 (P = 0.41)								
1.2.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention								
Engebretson 2013	7.69	1.267	257	7.69	1.267	257	13.7%	0.00 [-0.22 , 0.22]
Subtotal (95% CI)			**257**			**257**	**13.7%**	**0.00 [-0.22 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
Total (95% CI)			**793**			**664**	**100.0%**	**-0.30 [-0.52 , -0.08]**
Heterogeneity: Tau² = 0.08; Chi² = 60.47, df = 12 (P < 0.00001); I² = 80%								
Test for overall effect: Z = 2.68 (P = 0.007)								
Test for subgroup differences: Chi² = 4.23, df = 2 (P = 0.12), I² = 52.7%								

Footnotes
(1) SGI + additional mechanical therapy
(2) Periodontal treatment described as "mechanical therapy"

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants
(D) Blinding of clinical operator
(E) Blinding of periodontal outcome assessor
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

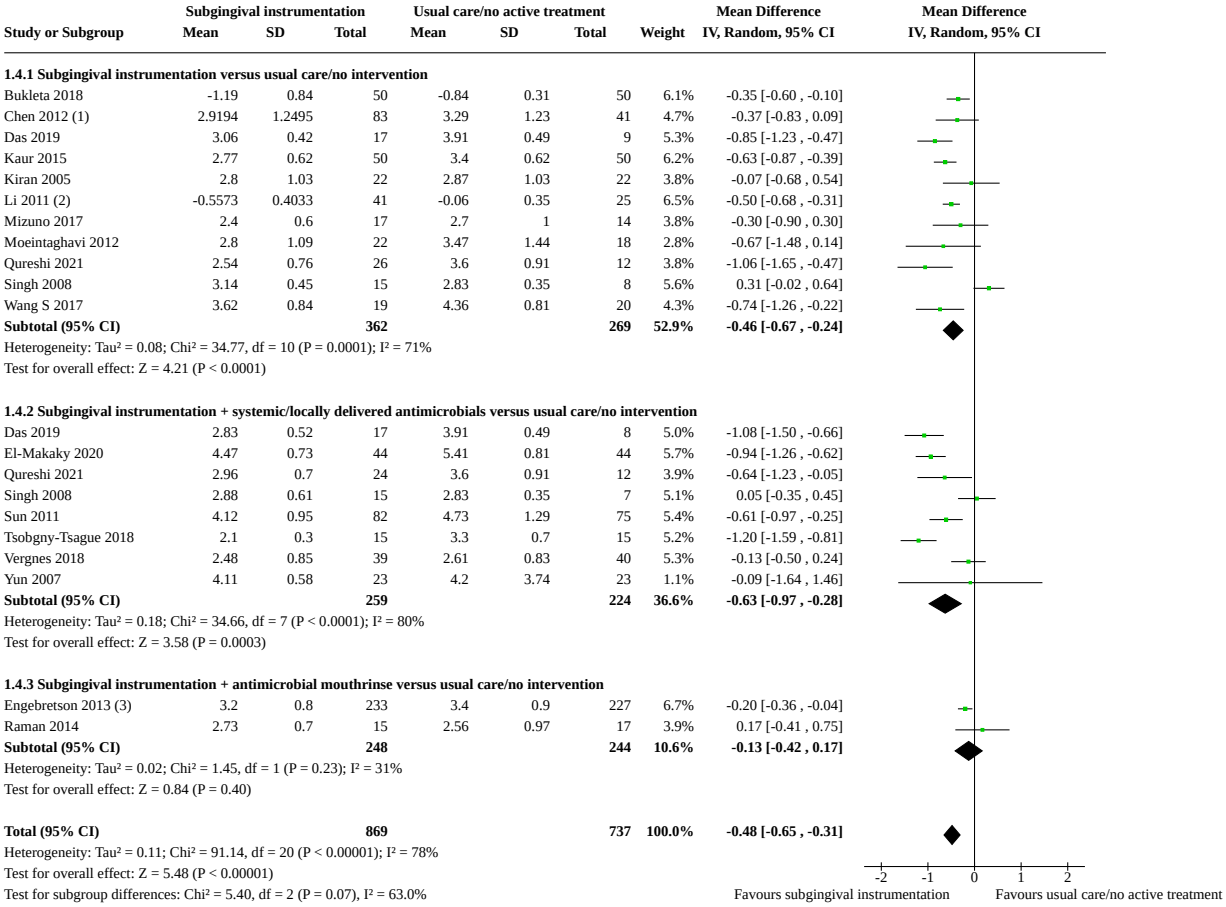
Analysis 1.3. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 3: HbA1c at 12 months



Study or Subgroup	Subgingival instrumentation Mean	SD	Total	Usual care/no active treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 Subgingival instrumentation versus usual care/ no intervention								
D'Aiuto 2018	7.8	0.2	133	8.3	0.2	131	100.0%	-0.50 [-0.55 , -0.45]
Subtotal (95% CI)			**133**			**131**	**100.0%**	**-0.50 [-0.55 , -0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 20.31 (P < 0.00001)								
Total (95% CI)			**133**			**131**	**100.0%**	**-0.50 [-0.55 , -0.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 20.31 (P < 0.00001)								
Test for subgroup differences: Not applicable								

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants
(D) Blinding of clinical operator
(E) Blinding of periodontal outcome assessor
(F) Incomplete outcome data (attrition bias)
(G) Selective reporting (reporting bias)
(H) Other bias

Analysis 1.4. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 4: CAL at 3-4 months

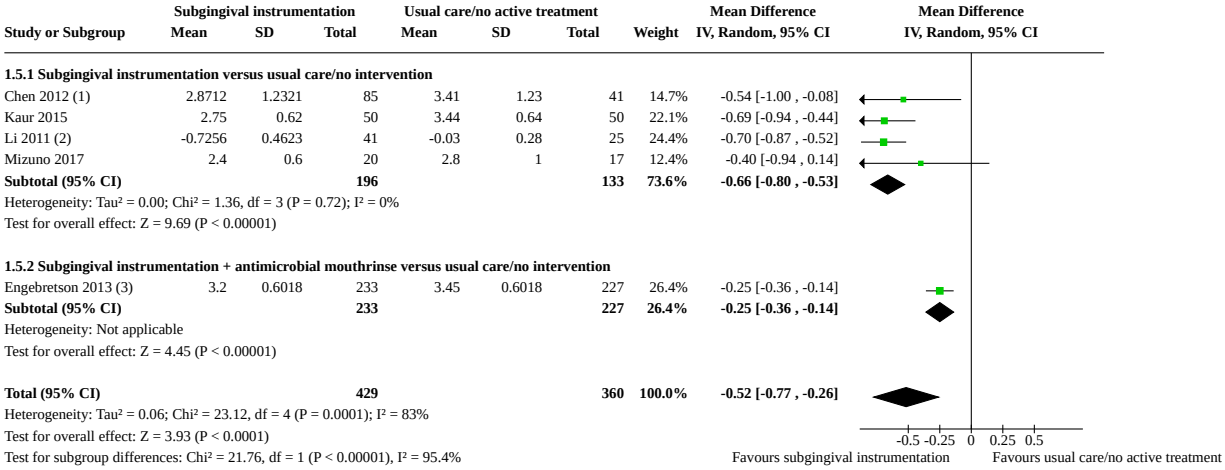


Study or Subgroup	Subgingival instrumentation Mean	SD	Total	Usual care/no active treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Subgingival instrumentation versus usual care/no intervention								
Bukleta 2018	-1.19	0.84	50	-0.84	0.31	50	6.1%	-0.35 [-0.60 , -0.10]
Chen 2012 (1)	2.9194	1.2495	83	3.29	1.23	41	4.7%	-0.37 [-0.83 , 0.09]
Das 2019	3.06	0.42	17	3.91	0.49	9	5.3%	-0.85 [-1.23 , -0.47]
Kaur 2015	2.77	0.62	50	3.4	0.62	50	6.2%	-0.63 [-0.87 , -0.39]
Kiran 2005	2.8	1.03	22	2.87	1.03	22	3.8%	-0.07 [-0.68 , 0.54]
Li 2011 (2)	-0.5573	0.4033	41	-0.06	0.35	25	6.5%	-0.50 [-0.68 , -0.31]
Mizuno 2017	2.4	0.6	17	2.7	1	14	3.8%	-0.30 [-0.90 , 0.30]
Moeintaghavi 2012	2.8	1.09	22	3.47	1.44	18	2.8%	-0.67 [-1.48 , 0.14]
Qureshi 2021	2.54	0.76	26	3.6	0.91	12	3.8%	-1.06 [-1.65 , -0.47]
Singh 2008	3.14	0.45	15	2.83	0.35	8	5.6%	0.31 [-0.02 , 0.64]
Wang S 2017	3.62	0.84	19	4.36	0.81	20	4.3%	-0.74 [-1.26 , -0.22]
Subtotal (95% CI)			**362**			**269**	**52.9%**	**-0.46 [-0.67 , -0.24]**
Heterogeneity: Tau² = 0.08; Chi² = 34.77, df = 10 (P = 0.0001); I² = 71%								
Test for overall effect: Z = 4.21 (P < 0.0001)								
1.4.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention								
Das 2019	2.83	0.52	17	3.91	0.49	8	5.0%	-1.08 [-1.50 , -0.66]
El-Makaky 2020	4.47	0.73	44	5.41	0.81	44	5.7%	-0.94 [-1.26 , -0.62]
Qureshi 2021	2.96	0.7	24	3.6	0.91	12	3.9%	-0.64 [-1.23 , -0.05]
Singh 2008	2.88	0.61	15	2.83	0.35	7	5.1%	0.05 [-0.35 , 0.45]
Sun 2011	4.12	0.95	82	4.73	1.29	75	5.4%	-0.61 [-0.97 , -0.25]
Tsobgny-Tsague 2018	2.1	0.3	15	3.3	0.7	15	5.2%	-1.20 [-1.59 , -0.81]
Vergnes 2018	2.48	0.85	39	2.61	0.83	40	5.3%	-0.13 [-0.50 , 0.24]
Yun 2007	4.11	0.58	23	4.2	3.74	23	1.1%	-0.09 [-1.64 , 1.46]
Subtotal (95% CI)			**259**			**224**	**36.6%**	**-0.63 [-0.97 , -0.28]**
Heterogeneity: Tau² = 0.18; Chi² = 34.66, df = 7 (P < 0.0001); I² = 80%								
Test for overall effect: Z = 3.58 (P = 0.0003)								
1.4.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention								
Engebretson 2013 (3)	3.2	0.8	233	3.4	0.9	227	6.7%	-0.20 [-0.36 , -0.04]
Raman 2014	2.73	0.7	15	2.56	0.97	17	3.9%	0.17 [-0.41 , 0.75]
Subtotal (95% CI)			**248**			**244**	**10.6%**	**-0.13 [-0.42 , 0.17]**
Heterogeneity: Tau² = 0.02; Chi² = 1.45, df = 1 (P = 0.23); I² = 31%								
Test for overall effect: Z = 0.84 (P = 0.40)								
Total (95% CI)			**869**			**737**	**100.0%**	**-0.48 [-0.65 , -0.31]**
Heterogeneity: Tau² = 0.11; Chi² = 91.14, df = 20 (P < 0.00001); I² = 78%								
Test for overall effect: Z = 5.48 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.40, df = 2 (P = 0.07), I² = 63.0%								

Footnotes

(1) SGI + additional mechanical therapy
(2) Periodontal treatment described as "mechanical therapy"
(3) Standard deviations estimated from baseline data

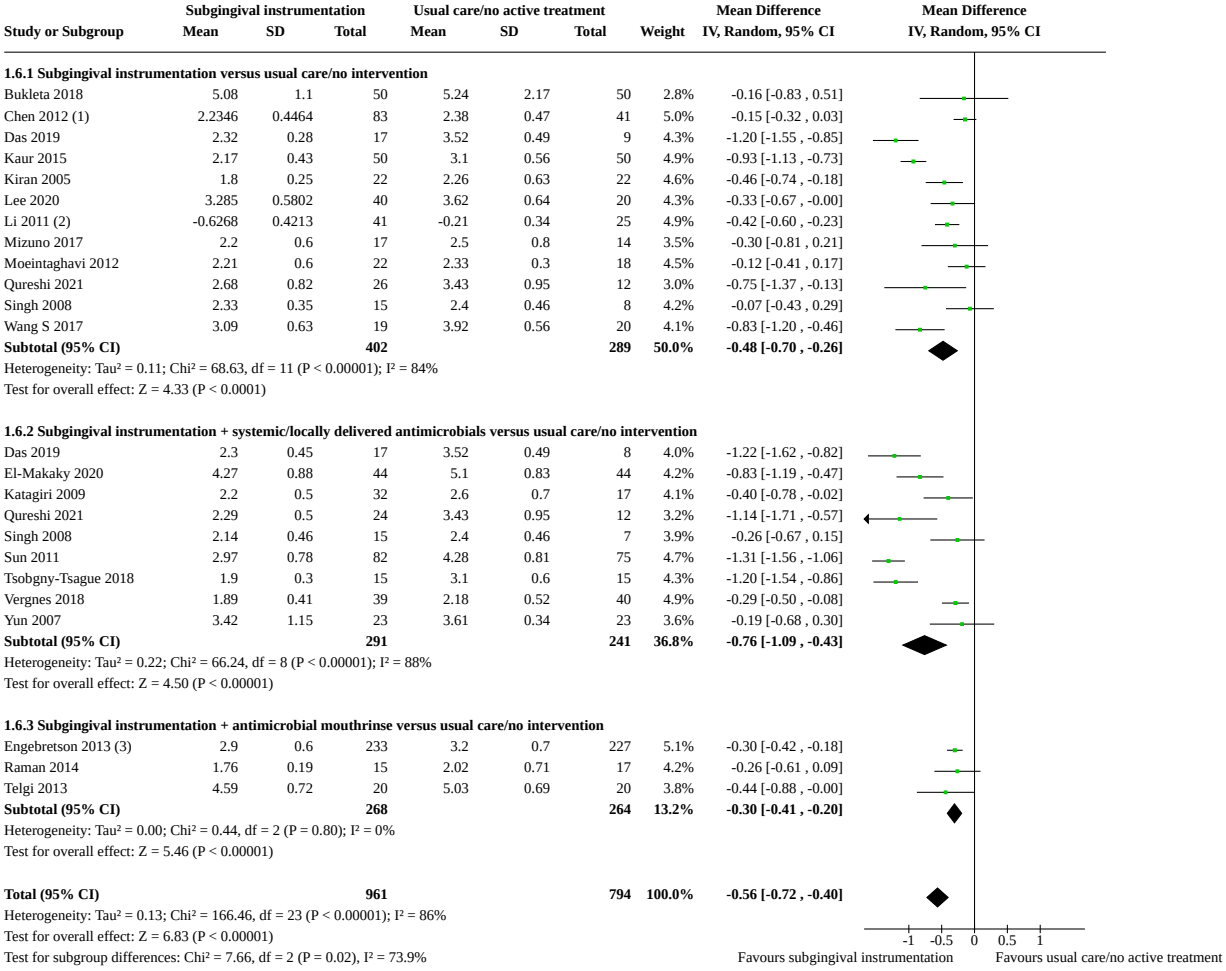
Analysis 1.5. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 5: CAL at 6 months



Footnotes

(1) SGI + additional mechanical therapy
(2) Periodontal treatment described as "mechanical therapy"
(3) Adjusted data used

Analysis 1.6. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 6: PPD at 3-4 months



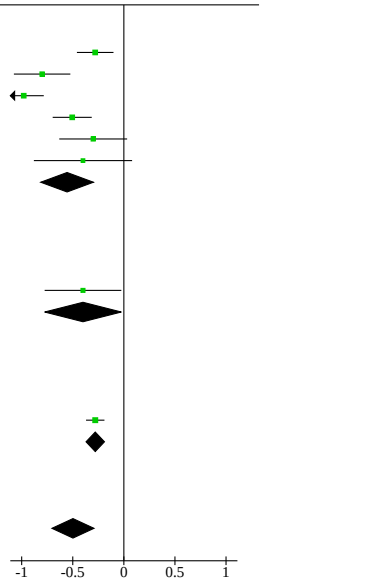
Study or Subgroup	Subgingival instrumentation Mean	SD	Total	Usual care/no active treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 Subgingival instrumentation versus usual care/no intervention								
Bukleta 2018	5.08	1.1	50	5.24	2.17	50	2.8%	-0.16 [-0.83 , 0.51]
Chen 2012 (1)	2.2346	0.4464	83	2.38	0.47	41	5.0%	-0.15 [-0.32 , 0.03]
Das 2019	2.32	0.28	17	3.52	0.49	9	4.3%	-1.20 [-1.55 , -0.85]
Kaur 2015	2.17	0.43	50	3.1	0.56	50	4.9%	-0.93 [-1.13 , -0.73]
Kiran 2005	1.8	0.25	22	2.26	0.63	22	4.6%	-0.46 [-0.74 , -0.18]
Lee 2020	3.285	0.5802	40	3.62	0.64	20	4.3%	-0.33 [-0.67 , -0.00]
Li 2011 (2)	-0.6268	0.4213	41	-0.21	0.34	25	4.9%	-0.42 [-0.60 , -0.23]
Mizuno 2017	2.2	0.6	17	2.5	0.8	14	3.5%	-0.30 [-0.81 , 0.21]
Moeintaghavi 2012	2.21	0.6	22	2.33	0.3	18	4.5%	-0.12 [-0.41 , 0.17]
Qureshi 2021	2.68	0.82	26	3.43	0.95	12	3.0%	-0.75 [-1.37 , -0.13]
Singh 2008	2.33	0.35	15	2.4	0.46	8	4.2%	-0.07 [-0.43 , 0.29]
Wang S 2017	3.09	0.63	19	3.92	0.56	20	4.1%	-0.83 [-1.20 , -0.46]
Subtotal (95% CI)			**402**			**289**	**50.0%**	**-0.48 [-0.70 , -0.26]**
Heterogeneity: Tau² = 0.11; Chi² = 68.63, df = 11 (P < 0.00001); I² = 84%								
Test for overall effect: Z = 4.33 (P < 0.0001)								
1.6.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention								
Das 2019	2.3	0.45	17	3.52	0.49	8	4.0%	-1.22 [-1.62 , -0.82]
El-Makaky 2020	4.27	0.88	44	5.1	0.83	44	4.2%	-0.83 [-1.19 , -0.47]
Katagiri 2009	2.2	0.5	32	2.6	0.7	17	4.1%	-0.40 [-0.78 , -0.02]
Qureshi 2021	2.29	0.5	24	3.43	0.95	12	3.2%	-1.14 [-1.71 , -0.57]
Singh 2008	2.14	0.46	15	2.4	0.46	7	3.9%	-0.26 [-0.67 , 0.15]
Sun 2011	2.97	0.78	82	4.28	0.81	75	4.7%	-1.31 [-1.56 , -1.06]
Tsobgny-Tsague 2018	1.9	0.3	15	3.1	0.6	15	4.3%	-1.20 [-1.54 , -0.86]
Vergnes 2018	1.89	0.41	39	2.18	0.52	40	4.9%	-0.29 [-0.50 , -0.08]
Yun 2007	3.42	1.15	23	3.61	0.34	23	3.6%	-0.19 [-0.68 , 0.30]
Subtotal (95% CI)			**291**			**241**	**36.8%**	**-0.76 [-1.09 , -0.43]**
Heterogeneity: Tau² = 0.22; Chi² = 66.24, df = 8 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 4.50 (P < 0.00001)								
1.6.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention								
Engebretson 2013 (3)	2.9	0.6	233	3.2	0.7	227	5.1%	-0.30 [-0.42 , -0.18]
Raman 2014	1.76	0.19	15	2.02	0.71	17	4.2%	-0.26 [-0.61 , 0.09]
Telgi 2013	4.59	0.72	20	5.03	0.69	20	3.8%	-0.44 [-0.88 , -0.00]
Subtotal (95% CI)			**268**			**264**	**13.2%**	**-0.30 [-0.41 , -0.20]**
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%								
Test for overall effect: Z = 5.46 (P < 0.00001)								
Total (95% CI)			**961**			**794**	**100.0%**	**-0.56 [-0.72 , -0.40]**
Heterogeneity: Tau² = 0.13; Chi² = 166.46, df = 23 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 6.83 (P < 0.00001)								
Test for subgroup differences: Chi² = 7.66, df = 2 (P = 0.02), I² = 73.9%								

Footnotes

(1) SGI + additional mechanical therapy
(2) Periodontal treatment described as "mechanical therapy"
(3) Standard deviations estimated from baseline data

Analysis 1.7. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 7: PPD at 6 months

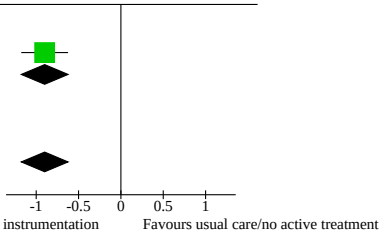
Study or Subgroup	SRP Mean	SRP SD	SRP Total	Usual care/no active treatment Mean	Usual care/no active treatment SD	Usual care/no active treatment Total	Weight	Mean Difference IV, Random, 95% CI
1.7.1 Subgingival instrumentation versus usual care/no intervention								
Chen 2012 (1)	2.1395	0.436	85	2.42	0.5	41	14.2%	-0.28 [-0.46 , -0.10]
D'Aiuto 2018	2.9	1.15	133	3.7	1.14	131	12.4%	-0.80 [-1.08 , -0.52]
Kaur 2015	2.15	0.42	50	3.13	0.57	50	13.9%	-0.98 [-1.18 , -0.78]
Li 2011 (2)	-0.7054	0.4347	41	-0.2	0.35	25	14.0%	-0.51 [-0.70 , -0.31]
Mauri-Obradors 2018 (3)	2.58	0.77	35	2.88	0.72	44	11.2%	-0.30 [-0.63 , 0.03]
Mizuno 2017	2.2	0.5	20	2.6	0.9	17	8.5%	-0.40 [-0.88 , 0.08]
Subtotal (95% CI)			**364**			**308**	**74.2%**	**-0.56 [-0.81 , -0.30]**
Heterogeneity: Tau² = 0.08; Chi² = 32.94, df = 5 (P < 0.00001); I² = 85%								
Test for overall effect: Z = 4.23 (P < 0.0001)								
1.7.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention								
Katagiri 2009	2.2	0.5	32	2.6	0.7	17	10.4%	-0.40 [-0.78 , -0.02]
Subtotal (95% CI)			**32**			**17**	**10.4%**	**-0.40 [-0.78 , -0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.09 (P = 0.04)								
1.7.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention								
Engebretson 2013 (4)	2.9	0.4924	233	3.18	0.4924	227	15.4%	-0.28 [-0.37 , -0.19]
Subtotal (95% CI)			**233**			**227**	**15.4%**	**-0.28 [-0.37 , -0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.10 (P < 0.00001)								
Total (95% CI)			**629**			**552**	**100.0%**	**-0.50 [-0.70 , -0.29]**
Heterogeneity: Tau² = 0.07; Chi² = 51.44, df = 7 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 4.75 (P < 0.00001)								
Test for subgroup differences: Chi² = 4.13, df = 2 (P = 0.13), I² = 51.6%								



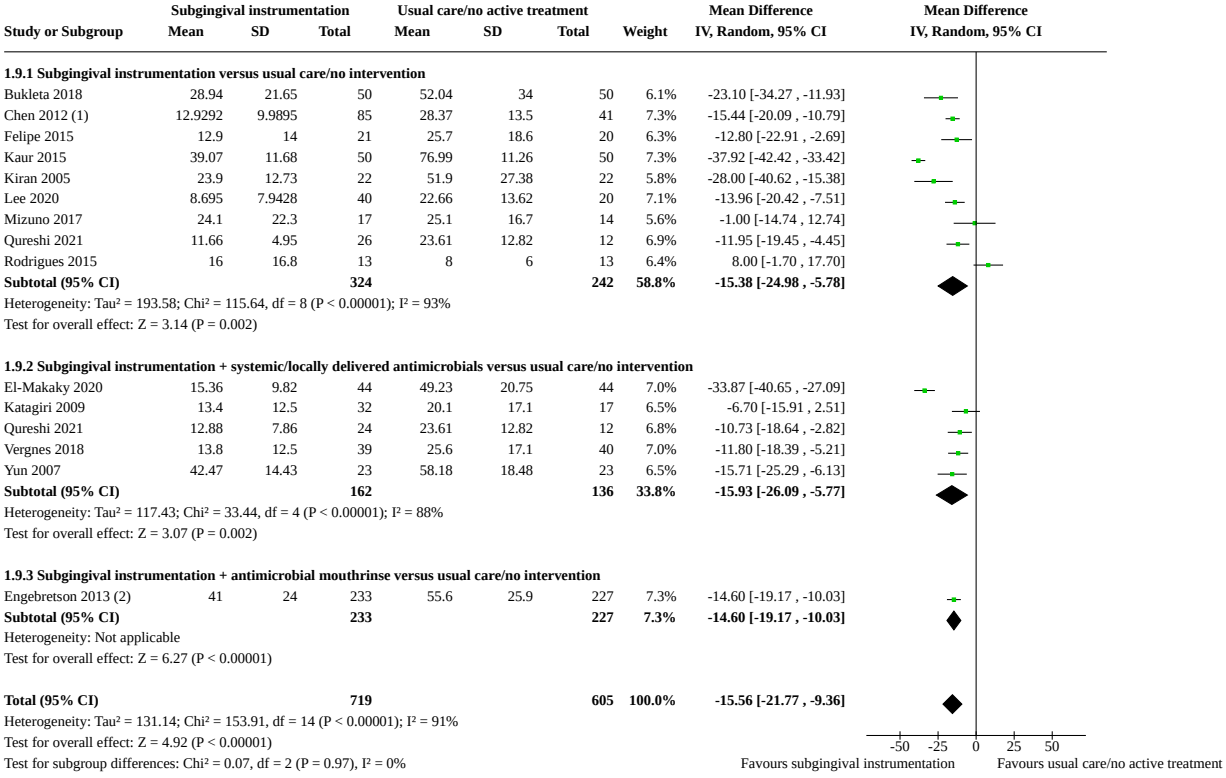
Footnotes
(1) SGI + additional mechanical therapy
(2) Periodontal treatment described as "mechanical therapy"
(3) Estimated from graph assuming 95% CI shown
(4) Adjusted data used

Analysis 1.8. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 8: PPD at 12 months

Study or Subgroup	SRP Mean	SRP SD	SRP Total	Usual care/no active treatment Mean	Usual care/no active treatment SD	Usual care/no active treatment Total	Weight	Mean Difference IV, Random, 95% CI
1.8.1 Subgingival instrumentation versus usual care/no intervention								
D'Aiuto 2018	2.7	1.15	133	3.6	1.14	131	100.0%	-0.90 [-1.18 , -0.62]
Subtotal (95% CI)			**133**			**131**	**100.0%**	**-0.90 [-1.18 , -0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.39 (P < 0.00001)								
Total (95% CI)			**133**			**131**	**100.0%**	**-0.90 [-1.18 , -0.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.39 (P < 0.00001)								
Test for subgroup differences: Not applicable								



Analysis 1.9. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 9: BOP at 3-4 months



Study or Subgroup	Subgingival instrumentation Mean	SD	Total	Usual care/no active treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 Subgingival instrumentation versus usual care/no intervention								
Bukleta 2018	28.94	21.65	50	52.04	34	50	6.1%	-23.10 [-34.27 , -11.93]
Chen 2012 (1)	12.9292	9.9895	85	28.37	13.5	41	7.3%	-15.44 [-20.09 , -10.79]
Felipe 2015	12.9	14	21	25.7	18.6	20	6.3%	-12.80 [-22.91 , -2.69]
Kaur 2015	39.07	11.68	50	76.99	11.26	50	7.3%	-37.92 [-42.42 , -33.42]
Kiran 2005	23.9	12.73	22	51.9	27.38	22	5.8%	-28.00 [-40.62 , -15.38]
Lee 2020	8.695	7.9428	40	22.66	13.62	20	7.1%	-13.96 [-20.42 , -7.51]
Mizuno 2017	24.1	22.3	17	25.1	16.7	14	5.6%	-1.00 [-14.74 , 12.74]
Qureshi 2021	11.66	4.95	26	23.61	12.82	12	6.9%	-11.95 [-19.45 , -4.45]
Rodrigues 2015	16	16.8	13	8	6	13	6.4%	8.00 [-1.70 , 17.70]
Subtotal (95% CI)			**324**			**242**	**58.8%**	**-15.38 [-24.98 , -5.78]**
Heterogeneity: Tau² = 193.58; Chi² = 115.64, df = 8 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 3.14 (P = 0.002)								
1.9.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention								
El-Makaky 2020	15.36	9.82	44	49.23	20.75	44	7.0%	-33.87 [-40.65 , -27.09]
Katagiri 2009	13.4	12.5	32	20.1	17.1	17	6.5%	-6.70 [-15.91 , 2.51]
Qureshi 2021	12.88	7.86	24	23.61	12.82	12	6.8%	-10.73 [-18.64 , -2.82]
Vergnes 2018	13.8	12.5	39	25.6	17.1	40	7.0%	-11.80 [-18.39 , -5.21]
Yun 2007	42.47	14.43	23	58.18	18.48	23	6.5%	-15.71 [-25.29 , -6.13]
Subtotal (95% CI)			**162**			**136**	**33.8%**	**-15.93 [-26.09 , -5.77]**
Heterogeneity: Tau² = 117.43; Chi² = 33.44, df = 4 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 3.07 (P = 0.002)								
1.9.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention								
Engebretson 2013 (2)	41	24	233	55.6	25.9	227	7.3%	-14.60 [-19.17 , -10.03]
Subtotal (95% CI)			**233**			**227**	**7.3%**	**-14.60 [-19.17 , -10.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.27 (P < 0.00001)								
Total (95% CI)			**719**			**605**	**100.0%**	**-15.56 [-21.77 , -9.36]**
Heterogeneity: Tau² = 131.14; Chi² = 153.91, df = 14 (P < 0.00001); I² = 91%								
Test for overall effect: Z = 4.92 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.07, df = 2 (P = 0.97), I² = 0%								

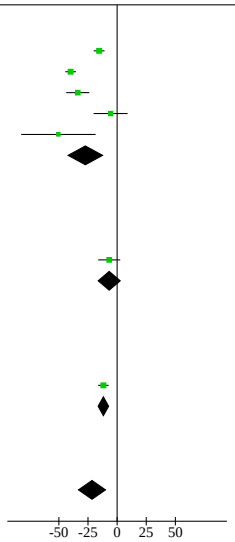
Footnotes

(1) SGI + additional mechanical treatment

(2) Standard deviation estimated from baseline data

Analysis 1.10. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 10: BOP at 6 months

Study or Subgroup	Subgingival instrumentation Mean	SD	Total	Usual care/no active treatment Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.10.1 Subgingival instrumentation versus usual care/no intervention								
Chen 2012 (1)	12.9292	9.9895	85	28.37	13.5	41	16.4%	-15.44 [-20.09 , -10.79]
Kaur 2015	38.96	11.62	50	78.88	11.84	50	16.4%	-39.92 [-44.52 , -35.32]
Koromantzos 2011 (2)	-38.12	22.53	30	-4.35	16.1	30	15.0%	-33.77 [-43.68 , -23.86]
Mizuno 2017	23.1	23.2	20	28.7	22	17	13.3%	-5.60 [-20.19 , 8.99]
Wang Y 2017	16	9.6	11	66.4	39.3	6	7.4%	-50.40 [-82.35 , -18.45]
Subtotal (95% CI)			**196**			**144**	**68.5%**	**-27.27 [-42.09 , -12.45]**
Heterogeneity: Tau² = 236.59; Chi² = 66.07, df = 4 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.61 (P = 0.0003)								
1.10.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention								
Katagiri 2009	12	11.4	32	18.8	18.1	17	15.1%	-6.80 [-16.27 , 2.67]
Subtotal (95% CI)			**32**			**17**	**15.1%**	**-6.80 [-16.27 , 2.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.41 (P = 0.16)								
1.10.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention								
Engebretson 2013	41.6	24	240	53.4	25.9	233	16.4%	-11.80 [-16.30 , -7.30]
Subtotal (95% CI)			**240**			**233**	**16.4%**	**-11.80 [-16.30 , -7.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.14 (P < 0.00001)								
Total (95% CI)			**468**			**394**	**100.0%**	**-21.57 [-33.18 , -9.96]**
Heterogeneity: Tau² = 208.54; Chi² = 108.84, df = 6 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 3.64 (P = 0.0003)								
Test for subgroup differences: Chi² = 5.25, df = 2 (P = 0.07), I² = 61.9%								



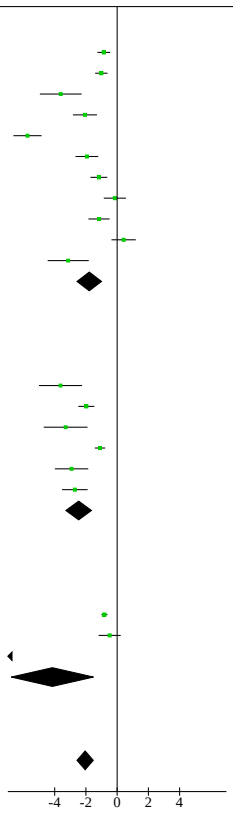
Footnotes

(1) SRP + additional mechanical therapy

(2) SRP + OHI vs mechanical treatment (supragingival cleaning) + OHI

Analysis 1.11. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 11: PI at 3-4 months

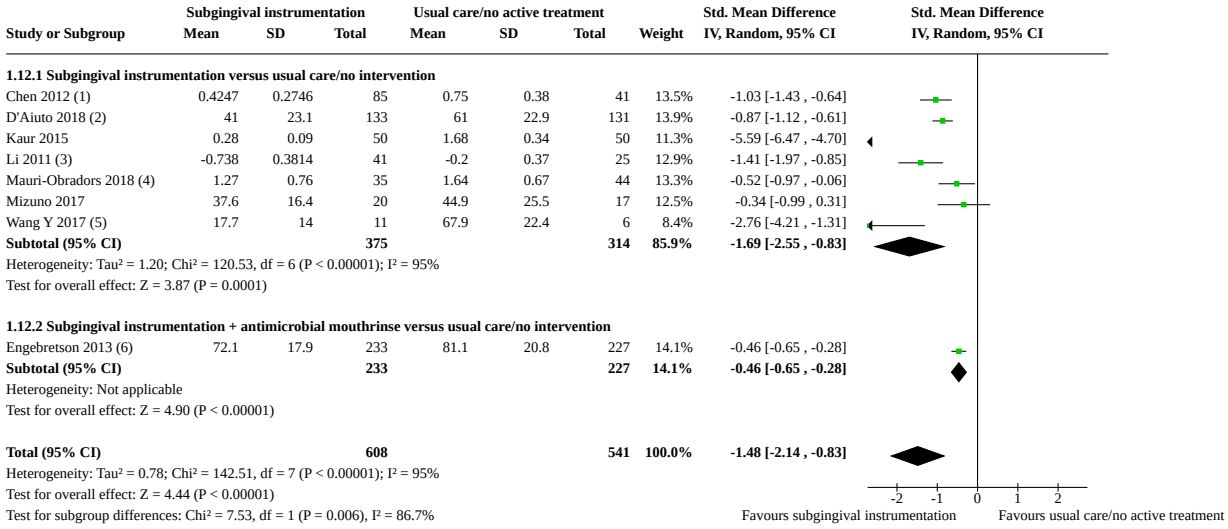
Study or Subgroup	Subgingival instrumentation Mean	SD	Total	Usual care/no active treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Subgingival instrumentation versus usual care/no intervention								
Bukleta 2018 (1)	57.8	22.7	50	77.88	23.79	50	5.8%	-0.86 [-1.27 , -0.45]
Chen 2012 (2)	0.4101	0.2804	83	0.74	0.4	41	5.8%	-1.01 [-1.41 , -0.61]
Das 2019 (2)	1.04	0.28	17	2.43	0.51	9	4.3%	-3.61 [-4.95 , -2.27]
Felipe 2015 (3)	23.9	17.7	21	65.9	22.1	20	5.3%	-2.06 [-2.83 , -1.29]
Kaur 2015 (2)	0.29	0.12	50	1.65	0.31	50	5.1%	-5.74 [-6.64 , -4.84]
Kiran 2005 (2)	0.29	0.17	22	1.54	0.88	22	5.4%	-1.94 [-2.66 , -1.21]
Li 2011 (4)	-0.7268	0.2301	41	-0.36	0.41	25	5.6%	-1.17 [-1.71 , -0.63]
Mizuno 2017	39.6	17.6	17	42.6	22.6	14	5.4%	-0.15 [-0.85 , 0.56]
Moeintaghavi 2012 (3)	63.22	21.13	22	87	18.7	18	5.4%	-1.16 [-1.84 , -0.48]
Rodrigues 2015	28.2	23.5	13	19.5	16.5	13	5.3%	0.41 [-0.36 , 1.19]
Singh 2008 (2)	0.83	0.15	15	1.52	0.3	8	4.3%	-3.14 [-4.45 , -1.82]
Subtotal (95% CI)			**351**			**270**	**57.7%**	**-1.79 [-2.57 , -1.00]**
Heterogeneity: Tau² = 1.59; Chi² = 154.66, df = 10 (P < 0.00001); I² = 94%								
Test for overall effect: Z = 4.46 (P < 0.00001)								
1.11.2 Subgingival instrumentation + systemic/locally delivered antimicrobials versus usual care/no intervention								
Das 2019	1.17	0.22	17	2.43	0.51	8	4.2%	-3.63 [-5.01 , -2.25]
El-Makaky 2020 (5)	16.64	10.21	44	49.5	21.02	44	5.7%	-1.97 [-2.48 , -1.46]
Singh 2008 (2)	0.86	0.12	15	1.52	0.3	7	4.2%	-3.30 [-4.70 , -1.90]
Sun 2011 (2)	1.43	0.67	82	2.18	0.69	75	5.8%	-1.10 [-1.43 , -0.76]
Tsobgny-Tsague 2018 (3)	18.1	15.1	15	63.7	15.3	15	4.8%	-2.92 [-3.99 , -1.85]
Yun 2007	1.57	0.43	23	3.04	0.62	23	5.2%	-2.71 [-3.53 , -1.89]
Subtotal (95% CI)			**196**			**172**	**29.9%**	**-2.46 [-3.28 , -1.64]**
Heterogeneity: Tau² = 0.82; Chi² = 36.68, df = 5 (P < 0.00001); I² = 86%								
Test for overall effect: Z = 5.89 (P < 0.00001)								
1.11.3 Subgingival instrumentation + antimicrobial mouthrinse versus usual care/no intervention								
Engebretson 2013 (6)	61.7	17.9	233	77.5	20.8	227	5.9%	-0.81 [-1.00 , -0.62]
Raman 2014 (7)	1.96	5.97	15	4.88	5.88	17	5.4%	-0.48 [-1.19 , 0.22]
Telgi 2013	1.05	0.04	20	1.86	0.04	20	1.0%	-19.85 [-24.47 , -15.23]
Subtotal (95% CI)			**268**			**264**	**12.4%**	**-4.15 [-6.78 , -1.51]**
Heterogeneity: Tau² = 4.35; Chi² = 65.98, df = 2 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 3.09 (P = 0.002)								
Total (95% CI)			**815**			**706**	**100.0%**	**-2.05 [-2.57 , -1.53]**
Heterogeneity: Tau² = 1.18; Chi² = 290.54, df = 19 (P < 0.00001); I² = 93%								
Test for overall effect: Z = 7.71 (P < 0.00001)								
Test for subgroup differences: Chi² = 3.57, df = 2 (P = 0.17), I² = 43.9%								



Footnotes

(1) Percentage score
(2) Silness-Loe Plaque Index 0-3
(3) Percentage
(4) Periodontal treatment described as "mechanical therapy"
(5) Percentage VPI
(6) Standard deviation estimated from baseline
(7) Percentage scores

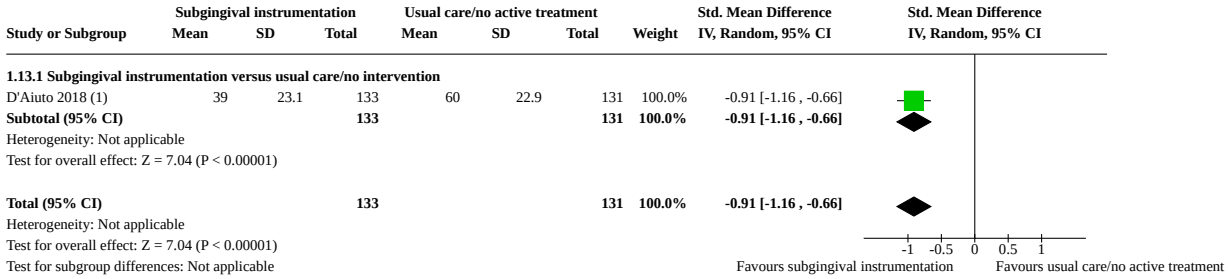
Analysis 1.12. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 12: PI at 6 months



Footnotes

(1) SGI + additional mechanical treatment
(2) Percentage sites
(3) Periodontal therapy described as "mechanical therapy"
(4) Estimated from graph assuming 95% CI shown
(5) Percentage of sites with plaque
(6) Standard deviation estimated from baseline data

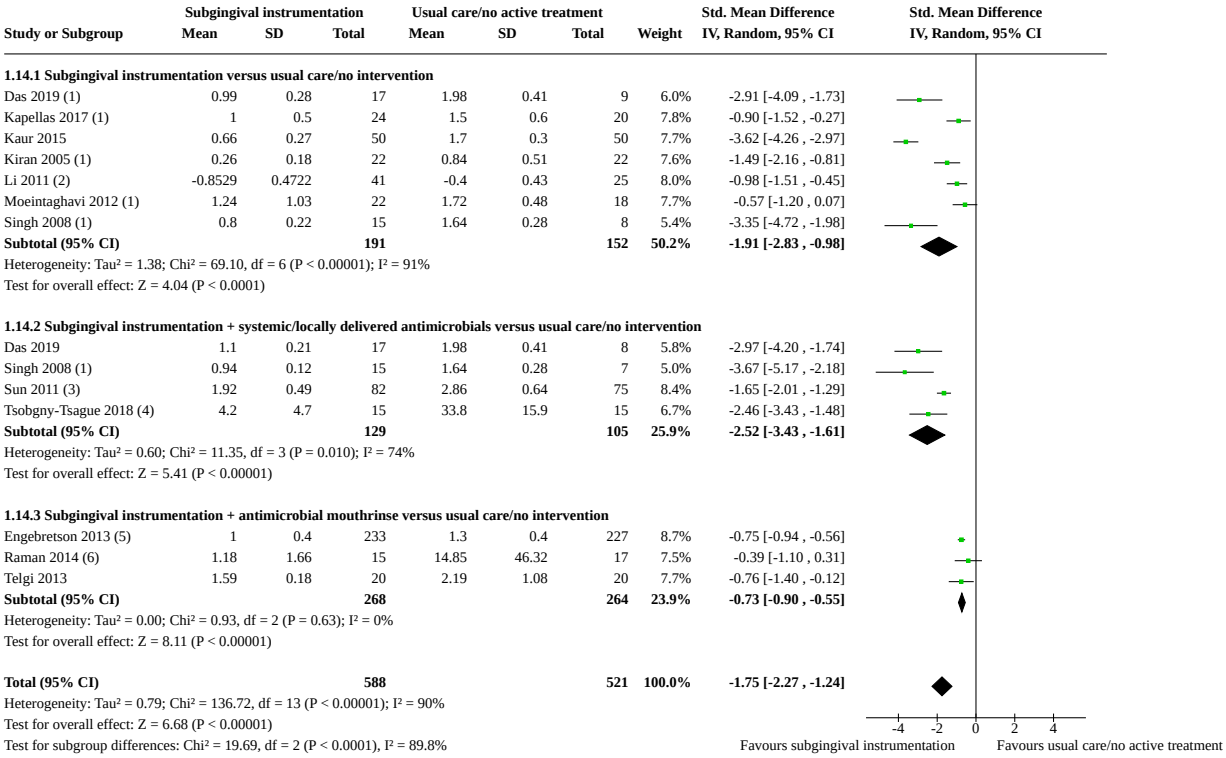
Analysis 1.13. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 13: PI at 12 months



Footnotes

(1) Percentage of sites with plaque

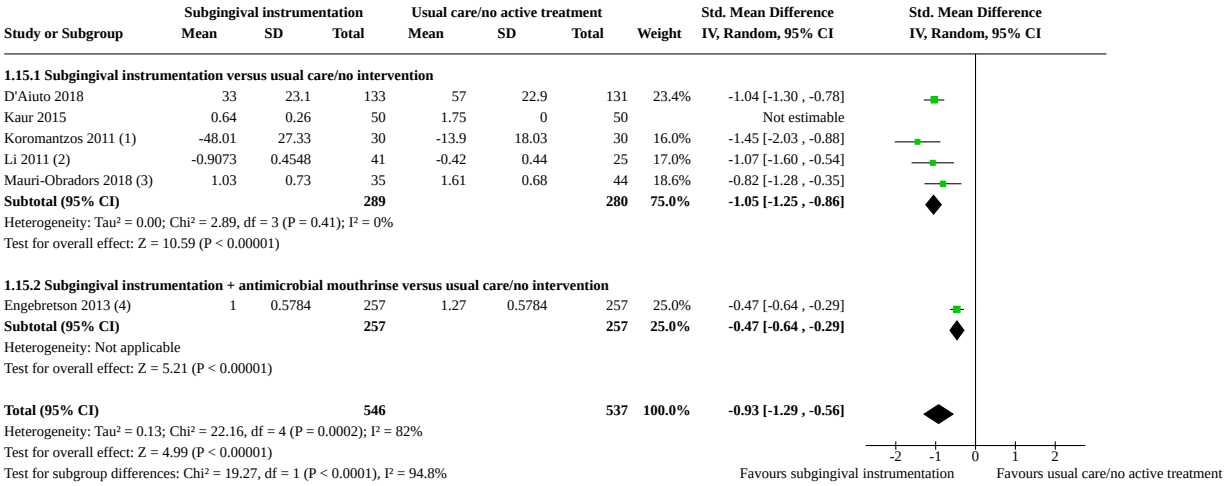
Analysis 1.14. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 14: GI at 3-4 months



Footnotes

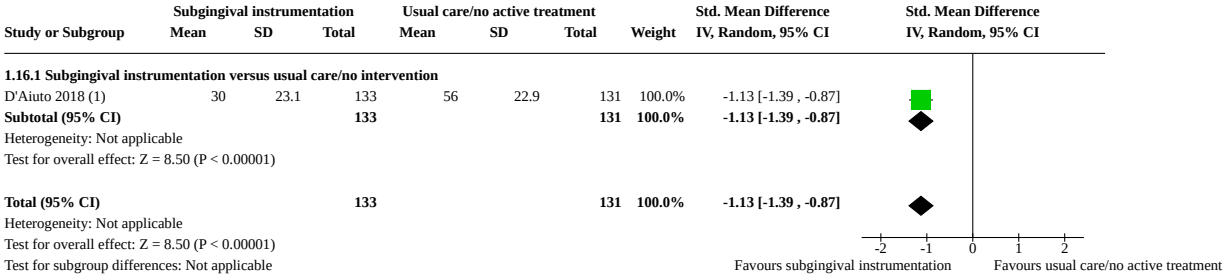
(1) Loe-Silness Gingival Index 0-3
(2) Periodontal treatment described as "mechanical therapy"
(3) Sulcus bleeding index 0-5
(4) Ainamo & Bay Gingival Bleeding Index - percentage score
(5) Standard deviation estimated from baseline data
(6) Gingival Bleeding Index - percentage

Analysis 1.15. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 15: GI at 6 months



Footnotes
(1) SRP + OHI vs mechanical therapy (supragingival cleaning) + OHI
(2) Periodontal treatment described as "mechanical therapy"
(3) Estimated from graph assuming 95% CI shown
(4) Adjusted data used

Analysis 1.16. Comparison 1: Periodontal treatment versus no active intervention/usual care, Outcome 16: GI at 12 months



Footnotes
(1) Percentage of sites with bleeding

ADDITIONAL TABLES

Table 1. Flow of studies in previous version of the review

Search results in previous version of the review (2015)
The literature search for this review update identified 688 records after the duplicates were removed. These 688 records were screened independently and in duplicate. After screening, we retained 74 records for further assessment and categorised 614 records as not relevant.
We tried to obtain full texts of 74 records, but only found 62 full-text articles as 12 studies were still ongoing. We also found two studies (Calbacho 2004; Singh 2008) in the bibliographies of reviews (Darré 2008; Engebretson 2013a; Sgolastra 2013).
Following our assessment of the 64 full-text articles (including Calbacho 2004 and Singh 2008) from this updated search, we excluded a total of 12 studies (12 articles) with reasons provided (in Characteristics of excluded studies section), and we categorised five studies (seven articles) as awaiting classification at the next update of this review once required information has been identified (Characteristics of studies awaiting classification).

Table 1. Flow of studies in previous version of the review *(Continued)*

We included 35 studies (a total of 45 articles, including seven already included studies from the previous version of the review), of which 34 studies (all except Madden 2008) provided useable data. Figure 1 shows the study selection process.

Table 2. Diagnostic criteria (diabetes mellitus and periodontitis)

Study	Diabetes assessment of patients for inclusion	Periodontitis assessment of patients for inclusion
Artese 2015	Diagnosed with type 2 DM using WHO diagnostic criteria	Generalised severe chronic periodontitis
Bukleta 2018	Diagnosed with type 2 DM	Quote: "clinical diagnosis of periodontal disease with at least one site with a Probing Depth (PD) ≥ 5 mm, two teeth with attachment loss ≥ 6 mm"
Calbacho 2005	Diagnosed with type 2 DM	Quote: "moderate chronic marginal periodontitis diagnosis"
Chen 2012	Diagnosed with type 2 DM for > 1 year	AAP criteria, with a ≥ 1 mm mean CAL
D'Aiuto 2018	Diagnosed with type 2 DM using WHO diagnostic criteria	Moderate to severe periodontitis (≥ 20 periodontal pockets with PPD of > 4 mm and marginal alveolar bone loss of > 30%)
Das 2019	Participants with type 2 DM	Moderate to severe periodontitis (where 30% or more of the teeth have ≥ 4 mm CAL)
El-Makaky 2020	Diagnosis of diabetes type 2 for more than 5 years	Quote: "Diagnosis of periodontitis based on the presence of 4 teeth as a minimum with at least one site with a CAL ≥3 mm and PPD ≥4 mm"
Engebretson 2013	Diagnosed with type 2 DM more than 3 months duration, an HbA1c value between 7.0% and < 9.0% at screening	CAL and PPD of at least 5 mm in 2 or more quadrants of the mouth
Felipe 2015	Diagnosis of type 2 DM by an endocrinologist	Severe chronic periodontitis using AAP diagnostic criteria
Gay 2014	Diagnosed with type 2 DM. HbA1c levels ≥ 6.5%; initial HbA1c values between 5.7% to 6.5% were included if they were taking hypoglycaemic medications (n = 16)	Severe chronic periodontitis according to AAP criteria
Jones 2007	Statement that inclusion depended on a repeat HbA1c of 8.5% or more	Community Periodontal Index of Treatment Need (CPITN) scores of ≥ 3 in at least 2 sextants
Kapellas 2017	Self-reported DM or when HbA1c ≥ 47.5 mmol/mol	Quote: "Moderate/severe periodontitis defined using the joint Centers for Disease Control and Prevention and American Academy of Periodontology case definition"
Katagiri 2009	Type 2 DM and HbA1c 6.5% to 10.0%	At least 2 pocket sites with PPD ≥ 4 mm

Table 2. Diagnostic criteria (diabetes mellitus and periodontitis) *(Continued)*

Kaur 2015	Diagnosis of type 2 DM	Clinical diagnosis of moderate or severe generalised chronic periodontitis
Kiran 2005	Diabetes - participants under treatment for type 2 DM with HbA1c in the range 6% to 8%	Not reported
Koromantzos 2011	Type 2 DM and HbA1c levels from 7% to 10%	At least 8 sites with PPD ≥ 6 mm and 4 sites with CAL ≥ 5 mm, distributed in at least 2 different quadrants
Kothiwale 2013	Type 2 DM with a minimum duration of 2 years	CPI (community periodontal index: PPD ≥ 4 mm) and LA (loss of attachment: CAL ≥ 4 mm) indices (as stated in Peter 2007)
Lee 2020	Diagnosed with type 2 DM using WHO diagnostic criteria	Quote: "teeth with sites with a PD >5 mm and attachment loss in at least 2 quadrants ... [with] BOP at these sites"
Li 2011	Type 2 DM	Not reported
Mauri-Obradors 2018	Type 2 DM diagnosed at least 1.5 years prior to the study	Generalised chronic periodontitis defined according to the AAP 1999 classification system
Mizuno 2017	Physician-diagnosed type 2 DM at least 2 months prior to the study	Mild to advanced chronic periodontitis as defined by Eke 2012
Moeintaghavi 2012	Diagnosis of type 2 DM with glycated haemoglobin (HbA1c) values over 7%	AAP criteria
Qureshi 2021	Quote: "HbA1c level ≥ 6.5% and < 14% at baseline with already diagnosed T2DM since ≥ 1 years"	Quote: "Moderate to severe periodontitis"
Raman 2014	Type 2 DM diagnosed at least 1 year prior to the study	PD 5 or more pockets of ≥ 5 mm and probing AL of ≥ 4 mm or more in at least 2 different quadrants which bled on probing
Rapone 2021	Diagnosis of type 2 DM	Diagnosis of periodontitis defined according to the International Workshop for a Classification of Periodontal Diseases and Conditions consensus report
Rodrigues 2015	Diagnosed with type 2 DM using WHO diagnostic criteria	Severe chronic periodontitis according to the AAP 1999 classification system
Singh 2008	Type 2 DM	≥ 30% teeth PD and CAL ≥ 4 mm at baseline
Sun 2011	Type 2 DM for over a year; HbA1c: 7.5% to 9.5%	> 20 teeth, PD > 5 mm, more than 30% teeth with AL > 4 mm, or over 60% teeth with PD > 4 mm and AL > 3 mm
Telgi 2013	Diagnosis of type 2 DM	Mild to moderate periodontitis (PD 4 mm to 5 mm)
Tsobgny-Tsague 2018	Quote: "Poorly controlled Type 2 DM patients"	Moderate to severe chronic periodontitis according to AAP-CDC 2012 diagnostic criteria
Vergnes 2018	Uncontrolled type 1 or type 2 DM (HbA1c 7.0% to 9.5%) diagnosed at least 1 year prior to inclusion	Quote: "diagnosis of periodontitis attested by the presence of at least four teeth with at least one probed site with a periodontal pocket depth (PPD) ≥4 mm and a clinical attachment level (CAL) ≥3 mm"

Table 2. Diagnostic criteria (diabetes mellitus and periodontitis) *(Continued)*

Wang S 2017	Quote: "patients with a diagnosis of T2DM for over one year by a grade three hospital"	Quote: "chronic periodontitis, ≥15 remaining teeth, and more than 30% of teeth with probing depths (PDs) ≥ 5 mm and attachment loss (AL) > 4 mm, or more than 60% of teeth with a PD > 4 mm and an AL ≥ 3 mm"
Wang Y 2017	Diagnosed with type 2 DM using WHO diagnostic criteria at least 5 years prior to study	Quote: "moderate to severe chronic periodontitis (Li 2009) were met, including over six 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"
Yun 2007	Newly diagnosed type 2 DM	Periodontal - PPD > or equal to 5 mm but < 8 mm in 1 site in 4 teeth or 2 different quadrants. No indication of CAL or alveolar bone loss
Zhang 2013	Type 2 DM for > 1 year; HbA1c level within 3 months before recruitment should at least be 5.5%	At least 4 teeth with PPD ≥ 5 mm, CAL ≥ 4 mm, and BOP, distributed in 2 or more oral quadrants

Study authors' inclusion criteria for diabetes and periodontitis.
AAP: American Academy of Periodontology; AL: attachment loss; BOP: bleeding on probing; CAL: clinical attachment level; DM: diabetes mellitus; GI: gingival index; mmol/mol: millimoles per mole; PD: pocket depth; PPD: probing pocket depth; WHO: World Health Organization.

Table 3. Subgroup analyses for setting

Setting	Number of studies	Effect size (95% CI)	Heterogeneity P value; I^2	P value from subgroup comparison
HbA1c measured at 3 to 4 months				
Secondary care	23	-0.48 (-0.67 to -0.30)	< 0.00001; 71%	
Community setting	3	-0.23 (-0.69 to 0.22)	0.002; 84%	
Primary care	2	-0.39 (-0.85 to 0.07)	0.58; 0%	
Overall	28	-0.45 (-0.61 to -0.28	< 0.00001; 72%	0.59
HbA1c measured at 6 months				
Secondary care	9	-0.37 (-0.66 to -0.08)	< 0.00001; 85%	
Community setting	2	-0.02 (-0.23 to 0.19)	0.42; 0%	
Overall	11	-0.31 (-0.54 to -0.07)	< 0.00001; 82%	0.06

CI: confidence interval.

Table 4. Subgroup analysis for periodontal treatment maintenance or not

Setting	Number of studies	Effect size (95% CI)	Heterogeneity P value; I^2	P value from subgroup comparison

Table 4. Subgroup analysis for periodontal treatment maintenance or not *(Continued)*

HbA1c measured at 6 months				
Maintenance	8	-0.23 (-0.45 to -0.01)	< 0.00001; 82%	
No maintenance	3	-0.06 (-0.60 to 0.47)	0.30; 16%	
Overall	10[a]	-0.21 (-0.41 to -0.01)	< 0.00001; 76%	0.58

[a] Chen 2012 was a 3-arm trial and contributed to both subgroups; the control group was divided in half to avoid double counting participants.
CI: confidence interval.

Table 5. Secondary outcomes: periodontal treatment versus no active intervention/usual care

Outcome	Time point	Number of studies	Mean difference (IV, 95% CI; P value)	Heterogeneity (P value; I^2)
CAL	3 to 4 months	18	-0.48, 95% CI -0.65 to -0.31 (Random); P < 0.00001	(P < 0.00001); I^2 = 78%
	6 months	5	-0.52, 95% CI -0.77 to -0.26 (Random); P < 0.0001	(P = 0.0001); I^2 = 83%
PPD	3 to 4 months	21	-0.56, 95% CI -0.72 to -0.40 (Random); P < 0.00001	(P < 0.00001); I^2 = 86%
	6 months	8	-0.50, 95% CI -0.70 to -0.29 (Random); P < 0.00001	(P < 0.00001); I^2 = 86%
	12 months	1	-0.90, 95% CI -1.18 to -0.62 (Random); P < 0.00001	NA
BOP	3 to 4 months	14	-15.56, 95% CI -21.77 to -9.36 (Random); P < 0.00001	(P < 0.00001); I^2 = 91%
	6 months	7	-21.57, 95% CI -33.18 to -9.96 (Random); P = 0.0003	(P < 0.00001); I^2 = 94%
PI	3 to 4 months	18	**SMD** -2.05, 95% CI -2.57 to -1.53 (Random); P < 0.00001	(P < 0.00001); I^2 = 93%
	6 months	8	**SMD** -1.48, 95% CI -2.14 to -0.83 (Random); P < 0.00001	(P < 0.00001); I^2 = 95%
	12 months	1	**SMD** -0.91, 95% CI -1.16 to -0.66 (Random); P < 0.00001	NA
GI	3 to 4 months	12	**SMD** -1.75, 95% CI -2.27 to -1.24 (Random); P < 0.00001	(P < 0.00001); I^2 = 90%
	6 months	6	**SMD** -0.93, 95% CI -1.29 to -0.56 (Random); P < 0.00001	(P = 0.0002); I^2 = 82%
	12 months	1	**SMD** -1.13, 95% CI -1.39 to -0.87 (Random); P < 0.00001	NA

BOP: bleeding on probing; CAL: clinical attachment level; CI: confidence interval; GI: gingival index; IV: inverse variance; NA: not applicable; PI: plaque index; PPD: probing pocket depth; SMD: standardised mean difference.

Table 6. Minor adverse effects in D'Aiuto 2018

Adverse effect	Numbers in intervention group	Numbers in control group
Tooth pain	43 (4.0%)	31 (3.0%)
Tooth infection	27 (2.5%)	27 (2.6%)
Tooth sensitivity	33 (3.1%)	9 (0.9%)
Vaccination	21 (2.0%)	24 (2.3%)
Chest infection	13 (1.2%)	11 (1.0%)
Gum swelling	12 (1.1%)	8 (0.8%)
Tooth fracture	12 (1.1%)	17 (1.6%)
Tooth restoration	9 (0.8%)	12 (1.1%)
Headache	8 (0.8%)	4 (0.4%)
Influenza	7 (0.7%)	7 (0.7%)
Throat infection	4 (0.4%)	5 (0.5%)
Foot infection	5 (0.5%)	6 (0.6%)
Fainting	3 (0.3%)	3 (0.3%)
Dizziness	4 (0.4%)	4 (0.4%)
Back pain	3 (0.3%)	5 (0.5%)
Frequency per group	≥ 1 TG 30 (23%) CG 23 (18%) ≥ 2 TG 33 (25%) CG 38 (29%) ≥ 3 TG 17 (13%) CG 18 (14%) ≥ 4 TG 12 (9%) CG 17 (13%) ≥ 5 TG 12 (9%) CG 6 (5%) ≥ 6 TG 7 (5%) CG 3 (2%) ≥ 7 TG 1 (1%) CG 3 (2%) ≥ 8 TG 3 (2%) CG 1 (1%)	

TG: treatment group; CG: control group.

APPENDICES

Appendix 1. Search strategies for the identification of studies

Cochrane Oral Health's Trials Register search strategy

Cochrane Oral Health's Trials Register is available via the Cochrane Register of Studies. For information on how the register is compiled, see oralhealth.cochrane.org/trials.

From April 2013, searches of the Cochrane Oral Health Trials Register were carried out in the Cochrane Register of Studies using the search strategy below:

#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's Trials Register were carried out using the Procite software and the search strategy below:

((diabet* or IDDM OR DMI OR MODY OR DM2 OR NIDDM OR IIDM)and periodont*)

Cochrane Central Register of Controlled Clinical 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)
#4 (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 PERIODONTAL DISEASES 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 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$.ti,ab. [mp=title, original title, abstract, name of substance word, subject heading word]
10. (("typ$ 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$) adj6 (DM or DM2)).ti,ab.
15. exp Insulin Resistance/
16. (insulin$ 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$).ti,ab.
20. or/1-19
21. exp Periodontics/
22. exp Periodontal Diseases/
23. exp Preventive Dentistry/
24. exp Dental Care for Chronically Ill/
25. periodont$.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 search was linked with the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials in MEDLINE (as described in Lefebvre 2020, box 3b).

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 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$).ti,ab.
20. or/1-19
21. exp Periodontics/
22. exp Periodontal Disease/
23. exp Preventive Dentistry/
24. Dental Care.mp. and Chronic$ 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 with the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials in Embase (as described in Lefebvre 2020, box 3e).

1. Randomized controlled trial/
2. Controlled clinical study/
3. random$.ti,ab.
4. randomization/
5. intermethod comparison/
6. placebo.ti,ab.
7. (compare or compared or comparison).ti.
8. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
9. (open adj label).ti,ab.
10. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab.

11. double blind procedure/
12. parallel group$1.ti,ab.
13. (crossover or cross over).ti,ab.
14. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant $1)).ti,ab.
15. (assigned or allocated).ti,ab.
16. (controlled adj7 (study or design or trial)).ti,ab.
17. (volunteer or volunteers).ti,ab.
18. human experiment/
19. trial.ti.
20. or/1-19
21. random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
22. Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
23. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
24. (Systematic review not (trial or study)).ti.
25. (nonrandom$ not random$).ti,ab.
26. "Random field$".ti,ab.
27. (random cluster adj3 sampl$).ti,ab.
28. (review.ab. and review.pt.) not trial.ti.
29. "we searched".ab. and (review.ti. or review.pt.)
30. "update review".ab.
31. (databases adj4 searched).ab.
32. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
33. Animal experiment/ not (human experiment/ or human/)
34. or/21-33
35. 20 not 34

CINAHL 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 PERIODONTAL DISEASES 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 with the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials in CINAHL (as described in Lefebvre 2020, box 3f).

S1 MH randomized controlled trials
S2 MH double-blind studies
S3 MH single-blind studies
S4 MH random assignment
S5 MH pretest-posttest design
S6 MH cluster sample
S7 TI (randomised OR randomized)
S8 AB (random*)
S9 TI (trial)
S10 MH (sample size) AND AB (assigned OR allocated OR control)
S11 MH (placebos)
S12 PT (randomized controlled trial)
S13 AB (control W5 group)
S14 MH (crossover design) OR MH (comparative studies)
S15 AB (cluster W3 RCT)
S16 MH animals+
S17 MH (animal studies)
S18 TI (animal model*)
S19 S16 OR S17 OR S18
S20 MH (human)
S21 S19 NOT S20
S22 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
S23 S22 NOT S21

LILACS BIREME Virtual Health Library search strategy

diabet$ [Palavras]

and periodont$ [Palavras]

This subject search was linked to the Brazilian Cochrane Center filter for LILACs BIREME:

((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) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple $ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal)))and not (Ct ANIMAL AND NOT (Ct HUMAN and Ct ANIMAL)))

ISI Web of Knowledge Conference Proceedings search strategy

diabet* AND periodont*

ZETOC 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 2. Search strategies for the identification of economic evidence

MEDLINE and Embase (via Ovid)

Search date: 2 March 2022

This search incorporates the Scottish Intercollegiate Guidelines Network (SIGN) filter for identifying economic evidence in Ovid MEDLINE (SIGN 2022).

1	exp Diabetes Mellitus/	1603368
2	diabet$.ab,ti.	1795819
3	(DKA or IDDM).mp. or DMI.ab,ti. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	33730
4	(MODY or DM2 or NIDDM).mp. or IIDM.ti,ab. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	26261
5	insulin$ secret$ dysfunc$.ti,ab.	199
6	insulin$ resist$.ti,ab.	224568
7	((impaired glucose tolerance or glucose intoleran$ or insulin$ resist$) and (DM or DM2)).ti,ab.	8185
8	insulin$ depend$.mp. or insulin?depend$.ti,ab. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	435057
9	(non insulin$ depend$ or nonisulin$ depend$ or nonisulin?depend).mp. or non insulin?depend$.ti,ab. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	307574
10	(("typ$ 1" or typ$ I) adj6 DM).ti,ab.	6911
11	(("typ$ 2" or typ$ II) adj6 DM).ti,ab.	17959
12	((juvenil$ or child$ or keto$ or labil$ or brittl$ or earl$ onset) adj6 (DM or DM1)).ti,ab.	3097
13	((keto$ prone or autoimmun$ or auto immun$ or sudden onset) adj6 (DM or DM1)).ti,ab.	1022
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.	929
15	exp Insulin Resistance/	226981

(Continued)

16	(insulin$ defic$ adj6 (absolut$ or relativ$)).ti,ab.	980
17	metabolic$ syndrom$.ti,ab.	146454
18	(syndrom$ X not (fragil$ X or X linked)).ti,ab.	3594
19	(plurimetabolic$ syndrom$ or pluri metabolic$ syndrom$).ti,ab.	95
20	or/1-19	2306628
21	exp Periodontics/	39945
22	exp Periodontal Diseases/	208333
23	exp Preventive Dentistry/	46299
24	exp Dental Care for Chronically Ill/	206300
25	periodont$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	228658
26	Surgical Flaps/	65836
27	surgical flap$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	67908
28	(26 or 27) and periodont$.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	2840
29	exp Dental Prophylaxis/	10160
30	(scale$ adj4 polish$).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	512
31	(scaling adj4 polish$).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	372
32	((root$ adj4 planing) or (root$ adj4 plan$)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	155987
33	(gingivitis or gingiva$).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	154111
34	((tooth adj6 scaling) or (teeth adj6 scaling) or (dental adj6 scaling)).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	6208
35	(((tooth adj6 scale$) or teeth) adj6 scale$).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	1336
36	(((oral adj3 prophylaxis) or dental) adj3 prophylaxis).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	10962
37	Oral Hygiene/	40246
38	Oral Health/	204806

(Continued)

39	(oral hygien$ or oral health$).mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm, ox, px, rx, ui, sy]	99540
40	or/21-25	491152
41	or/28-40	909856
42	or/40-41	909856
43	20 and 42	30743
44	Economics/	273757
45	"costs and cost analysis"/	109101
46	Cost allocation/	65972
47	Cost benefit analysis/	178385
48	Cost control/	94144
49	Cost savings/	78016
50	Cost of illness/	50902
51	Cost sharing/	66621
52	"deductibles and coinsurance"/	65781
53	Medical savings accounts/	557
54	Health care costs/	215095
55	Direct service costs/	208624
56	Drug costs/	95905
57	Employer health costs/	208504
58	Hospital costs/	35352
59	Health expenditures/	209638
60	Capital expenditures/	209407
61	Value of life/	157672
62	exp economics, hospital/	991560
63	exp economics, medical/	980379
64	Economics, nursing/	41091
65	Economics, pharmaceutical/	11841
66	exp "fees and charges"/	74984

(Continued)

67	exp budgets/	45805
68	(low adj cost).mp.	154919
69	(high adj cost).mp.	40156
70	(health?care adj cost$).mp.	39045
71	(fiscal or funding or financial or finance).tw.	422048
72	(cost adj estimate$).mp.	6437
73	(cost adj variable).mp.	121
74	(unit adj cost$).mp.	7970
75	(economic$ or pharmacoeconomic$ or price$ or pricing).tw.	823022
76	or/44-75	2652895
77	43 and 76	2801
78	limit 77 to yr="2000 -Current"	2704
79	limit 78 to english language	2650
80	remove duplicates from 79	2445
81	limit 80 to conference abstracts [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update,Ovid MEDLINE(R) PubMed not MEDLINE,Ovid MEDLINE(R) In-Process,Ovid MEDLINE(R) Publisher; records were retained]	1482
82	80 not 81	963

NHS EED via Ovid

Search date: 2 March 2022

1	exp Diabetes Mellitus, Type 2/ or exp Diabetes Mellitus, Type 1/ or exp Diabetes Mellitus/
2	diabet$.mp. [mp=title, text, subject heading word]
3	(DKA or IDDM).mp. [mp=title, text, subject heading word]
4	(MODY or DM2 or NIDDM).mp. [mp=title, text, subject heading word]
5	insulin$ secret$ dysfunc$.mp. [mp=title, text, subject heading word]
6	insulin$ resist$.mp. [mp=title, text, subject heading word]
7	(("typ$ 1" or typ$ I) adj6 DM).mp. [mp=title, text, subject heading word]
8	(("typ$ 2" or typ$ II) adj6 DM).mp. [mp=title, text, subject heading word]

(Continued)

9	or/1-8
10	exp Periodontics/
11	exp Periodontal Diseases/
12	exp Dental Care/
13	periodont$.mp. [mp=title, text, subject heading word]
14	Surgical Flaps/
15	(scale$ adj4 polish$).mp. [mp=title, text, subject heading word]
16	(scaling$ adj4 polish$).mp. [mp=title, text, subject heading word]
17	(root$ adj4 plan$).mp. [mp=title, text, subject heading word]
18	(gingivitis or gingiva$).mp. [mp=title, text, subject heading word]
19	(tooth adj6 scal$).mp. [mp=title, text, subject heading word]
20	((oral adj3 prophylaxis) or (dental adj3 prophylaxis)).mp. [mp=title, text, subject heading word]
21	Oral Hygiene/
22	Oral Health/
23	(oral hygien$ or oral health$).mp. [mp=title, text, subject heading word]
24	or/10-23
25	9 and 24

WHAT'S NEW

Date	Event	Description
15 March 2022	New citation required and conclusions have changed	The evidence certainty is now moderate that periodontal treatment improves glycaemic control in people with diabetes at time points up to 12 months
7 September 2021	New search has been performed	Search updated

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 5, 2010

Date	Event	Description
13 March 2018	Amended	Minor typographical error corrected in references (Firatli). Minor numerical error corrected in characteristics of included studies table (Santos 2009)
5 November 2015	New search has been performed	Search run up to December 2014
5 November 2015	New citation required but conclusions have not changed	Review now contains 35 included studies. The previous version (2010) had 7 included studies. New authors involved

CONTRIBUTIONS OF AUTHORS

All review authors other than Dwayne Boyers (DB) contributed to the main study selection, data extraction, risk of bias assessments, and updating of the background and discussion text. Data analysis and interpretation and GRADE assessment were undertaken by Helen Worthington, Terry Simpson, Joshua Twigg, Laura MacDonald, and Jan Clarkson. DB searched for economic analyses and interpreted and summarised relevant studies in a brief economic commentary.

DECLARATIONS OF INTEREST

- Terry C Simpson: none known.
- Janet E Clarkson: none known. I am joint Co-ordinating Editor of Cochrane Oral Health and Director of the Scottish Dental Clinical Effectiveness Programme. I was not involved in conducting the editorial process for the review.
- Helen V Worthington: none known. I am an Editor with Cochrane Oral Health, and was previously Co-ordinating Editor. I was not involved in conducting the editorial process for the review.
- Laura MacDonald: none known. I am a Managing Editor with Cocrane Oral Health. I was not involved in conducting the editorial process for the review.
- Jo C Weldon: none known. I was previously a salaried member of staff with Cochrane Oral Health.
- Ian Needleman: I am involved in research investigating the patient perspective on the periodontitis-diabetes link. I am also a project member with NHS England regarding the commissioning standard guideline for oral health care in people with diabetes as well as clinical practice guideline groups for periodontal health with the European Federation of Periodontology and British Society of Periodontology. I lead the British Society of Periodontology Patient Forum and am an advisory group member of the UCL Centre for Co-Production in Health Research. I have received funding for research and consultancy from oral healthcare industry (GlaxoSmithKline, Procter and Gamble, BrickBuilt Technologies) not related to the topic of this systematic review. I am an Editor with Cochrane Oral Health. I was not involved in conducting the editorial process for the review.
- Sarah H Wild: I received an honorarium paid into my research account from Gilead for attending an advisory board on the epidemiology of non-alcoholic fatty liver disease in January 2020, and I attend meetings of the Scottish Study Group for Diabetes in the Young for which registration/accommodation/subsistence are subsidised by an unrestricted educational grant from Novo Nordisk.
- Zipporah Iheozor-Ejiofor: none known. I am an Editor with Cochrane Oral Health and was previously a salaried member of staff. I was not involved in conducting the editorial process for the review.
- Ambrina Qureshi: I was principal investigator for a study included in the review, which was funded by the National Research Program for Universities, Higher Education Commission, Islamabad, Pakistan.
- Andrew Walker: none known.
- Veena A Patel: none known.
- Dwayne Boyers: none known.
- Joshua Twigg: none known.

SOURCES OF SUPPORT

Internal sources

- School of Dentistry, The University of Manchester, UK

  Support to Cochrane Oral Health.
- Manchester Academic Health Sciences Centre (MAHSC) and the NIHR Manchester Biomedical Research Centre, UK

  Support to Cochrane Oral Health.

- University College London, Eastman Dental Institute, UK

  Support to Ian Needleman.

External sources

- National Institute for Health and Care Research (NIHR), UK

  This project was supported by the NIHR, via Cochrane Infrastructure funding to Cochrane Oral Health. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Evidence Synthesis Programme, the NIHR, the NHS, or the Department of Health and Social Care.
- Cochrane Oral Health Global Alliance, Other

  The production of Cochrane Oral Health reviews has been supported financially by our Global Alliance since 2011 (oralhealth.cochrane.org/partnerships-alliances). Contributors in recent years have been the American Association of Public Health Dentistry, USA; AS-Akademie, Germany; the British Association for the Study of Community Dentistry, UK; the British Society of Paediatric Dentistry, UK; the Canadian Dental Hygienists Association, Canada; the Centre for Dental Education and Research at All India Institute of Medical Sciences, India; the National Center for Dental Hygiene Research & Practice, USA; New York University College of Dentistry, USA; and Swiss Society of Endodontology, Switzerland.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this 2022 update, we made the following amendments from the 2015 version of the review.

- We divided the review into two parts. This is part 1, which is focused on comparison 1 only: periodontal treatment versus no/delayed treatment or usual care. We will cover comparison 2, head-to-head trials of different periodontal treatments, in part 2 of the review, to be completed in 2023.
- We noted that HbA1c can also be reported as millimoles per mole (mmol/mol) (as a percentage of total haemoglobin) and we converted percentages into mmol/mols for the key results presented in the summary sections of the review.
- We revisited risk of bias assessments from the last version and reinstated the domain of blinding of periodontal outcome assessors in our risk of bias assessment.
- We refined the list of subgroup analyses planned. We retained subgroup analysis by intervention and control type (but changing from two to three categories); type 1 versus type 2 diabetes; and good, fair, poor diabetes control. We added subgroup analyses based on primary care versus secondary care setting, and maintenance following initial periodontal treatment versus none (for studies lasting longer than 3 months).

For the 2015 update, we made the following amendments to the methods published in the protocol for this review.

- The original second objective (to identify whether further research is required in this area and if so, to identify the important research questions and appropriate study designs) and third objective (to investigate the various combinations of therapies used in treating periodontal disease in people with diabetes mellitus) have been removed as they are considered to be consequences of the outcome of the review.
- Periodontal treatment has been defined broadly to include any professionally-delivered intervention designed to reduce periodontal disease, and the criteria for types of interventions amended accordingly.
- Fructosamine has been deleted as an outcome measure because HbA1c is considered a more reliable and widely used measure of glycaemic control. Fructosamine (glycolated albumin) may be used as an indicator of glycaemic control over the previous 2 to 3 weeks in individuals who have atypical haemoglobin (e.g. sickle cell disease or thalassaemia), which does not form HbA1c.
- The previously vague secondary outcome 'oral hygiene' has been reworded as 'plaque indices.'
- Trials where participants have metabolic syndrome are specifically excluded from this review.
- Diagnostic assessment criteria for diabetes mellitus are now clearly stated.
- Periodontal outcome assessment was removed as a risk of bias domain, as it was agreed that the addition of periodontal outcome assessment misdirected attention from the primary focus (glycaemic control) of this review.

NOTES

This review partially updates one published in 2010 (Simpson 2010) and updated in 2015 (Simpson 2015). The original protocol for the review was published in 2004 (Simpson 2004).

INDEX TERMS

Medical Subject Headings (MeSH)

Dental Scaling; Diabetes Mellitus, Type 1 [*blood]; Diabetes Mellitus, Type 2 [*blood]; Glycated Hemoglobin A [metabolism]; Hyperglycemia [blood] [*therapy]; Oral Hygiene; Periodontal Diseases [blood] [*therapy]; Randomized Controlled Trials as Topic; Root Planing; Time Factors

MeSH check words

Humans