Low-Quality Evidence Suggests Scaling and Root Planing May Have a Minor, Short-Term Effect on Glycemic Control in Patients with Diabetes

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Original study being reviewed: Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. Simpson TC, Weldon JC, Worthington HV, et al. Cochrane Database Syst Rev 2015;11:CD004714.

Background

Uncontrolled diabetes is a known risk factor for periodontal disease, and evidence suggests that periodontal disease may have an adverse effect on glycemic control.

Clinical question

In patients with Type 1 or Type 2 diabetes, does periodontal therapy, compared with no active treatment or usual care, improve glycemic control?

Summary of methods and results

Seven databases were searched for randomized controlled trials (RCTs), and hand searching of journals and reference lists was performed. Two authors independently screened titles and abstracts, extracted data, and assessed risk of bias, with a third author arbitrating disagreements. Thirty-five RCTs were identified. These studies either compared nonsurgical periodontal therapy, defined as scaling and root planing (SRP) or mechanical therapy, with usual care or no active treatment, or compared different types of nonsurgical periodontal therapy. Low-quality evidence indicates that SRP reduces mean glycosylated hemoglobin (HbA1c) by 0.29 percentage points (95% confidence interval [CI]: 0.48% to 0.10% lower) at 3 to 4 months, and 0.02 percentage points (95% CI: 0.20% lower to 0.16% higher) at 6 months. The addition of antimicrobial therapy did not provide added benefit to SRP alone, with 0.00 percentage points change in HbA1c at 3 to 4 months (95% CI: 0.22% lower to 0.22% higher), and 0.04 percentage points lower HbA1c at 6 months (95% CI: 0.41% lower to 0.32% higher).

Critical appraisal

This was a well-conducted systematic review. However, pooling of data when comparing SRP with SRP + antimicrobial was questionable due to clinical heterogeneity (differing antimicrobial therapies). The overall evidence is of low quality. The magnitude of effect of SRP in reducing HbA1c is minor, short-term, and has unclear clinical relevance.

Practical implications

Because of concerns with the low quality of evidence and uncertain magnitude of effect, the results of this systematic review should be interpreted with caution. It remains prudent to manage periodontal disease in all patients, especially those with risk factors such as diabetes, as a recent American Dental Association (ADA) systematic review and guideline suggests that SRP is an effective management strategy for periodontal disease. However, it is uncertain if nonsurgical periodontal treatment will have a sustained and significant impact on glycemic control in patients with diabetes.

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Evidence summary

Background

Diabetes is a chronic disease that impacts the body's ability either to produce insulin (type 1) or use insulin (type 2). In the United States, 29.1 million people, or 9.3% of the population, have diabetes,[1] and the global cost of diabetes care is $612 billion.[2] There is a higher prevalence of diabetes in certain populations such as Hispanics (12.8%), non-Hispanic blacks (13.2%), and American Indians/Alaskan Natives (15.9%).[3] Glycemic control is critical for patients with diabetes to prevent complications such as diabetic retinopathy, peripheral neuropathy, coronary heart disease, cerebrovascular disease, and kidney failure.

Diabetes is one of many systemic diseases that are correlated with oral conditions such as periodontal disease.[4,5] It is important to consider that a correlation between conditions does not imply causality, as there may be other confounding factors that can impact both conditions in question. Nonetheless, uncontrolled diabetes is a known risk factor for periodontal disease.[6–8] Additionally, some evidence suggests that periodontal disease may have an adverse effect on glycemic control.[9–11] With this in mind, the authors conducted this systematic review to determine if periodontal therapy affects glycemic control in patients with diabetes.

Clinical question

In patients with type 1 or type 2 diabetes, does periodontal therapy, compared with no active treatment or usual care, improve glycemic control?

Methods

Seven databases were searched: Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, LILACS, CINAHL, and EBSCO. In addition, two databases were searched for conference proceedings (Web of Knowledge, ZETOC). Hand searching included two periodontal journals (*Annals of Periodontology*, *Periodontology 2000*) and reference lists of identified studies and known papers on the topic. Inclusion criteria were randomized controlled trials (RCTs) of patients with periodontitis and type 1 or type 2 diabetes with follow-up of at least 90 days after treatment completion, which measured glycosylated hemoglobin (HbA1c) as an outcome. Included interventions were mechanical debridement, surgical treatment, antimicrobial therapy, drug therapy, and other novel interventions to manage periodontal disease. Split-mouth and crossover studies were excluded due to possible carryover effects. Comparisons were periodontal therapy versus no active intervention, usual care, or placebo, or one periodontal therapy versus another.

Two authors independently screened titles and abstracts, extracted data, and assessed risk of bias. A third author arbitrated disagreements. The primary outcome assessed was HbA1c as a measurement of blood glucose level. Secondary outcomes were adverse effects, periodontal parameters (bleeding on probing [BOP], clinical attachment level [CAL], Gingival Index [GI], Plaque Index [PI], and probing pocket depth [PPD]), cost implications, and diabetic complications.

Risk of bias of included RCTs was assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0.[12] Criteria evaluated were: random sequence generation, allocation concealment, blinding of participants, blinding of clinical operator, incomplete outcome data, selective outcome reporting, and other biases. Funnel plots, Begg and Mazumdar adjusted rank correlation test, and the Egger et al regression asymmetry test were used to evaluate publication bias.

Since measurement of HbA1c is a continuous outcome, the mean difference between groups was calculated with 95% confidence interval (CI). Meta-analysis was conducted using a random-effects model when there were at least four studies. Statistical heterogeneity was quantified by the calculation of the I^2 statistic for heterogeneity. There were not a sufficient number of studies to conduct subgroup analyses. Sensitivity analysis was conducted to ensure the results were robust. GRADE[13] was used to assess the quality of the body of evidence with reference to overall risk of bias of the included studies, directness of the evidence, consistency of the results, precision of the estimates, risk of publication bias, and magnitude of the effect.

Results

Thirty-five RCTs with a total of 2,565 participants met the inclusion criteria. Of these studies, 33 evaluated only patients with type 2 diabetes and two evaluated those with type 1. The age of included subjects ranged from 18 to 80, and the follow-up ranged from 3 months to 1 year. Twenty-nine studies were at high risk of bias, two were at low risk, and four were unclear.

TABLE 1 AMSTAR Checklist

1. Was an a priori design provided?	**Yes.** The systematic review protocol was developed before the review was conducted.
2. Was study selection and data extraction done in duplicate?	**Yes.** Two authors independently screened titles and abstracts. For included studies, two authors conducted data extraction and assessed risk of bias. A third author acted as arbiter for any disagreements.
3. Was a comprehensive literature search performed?	**Yes.** The following databases were searched: Cochrane Oral Health Group Trials Register, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, LILACS, CINAHL, EBSCO. The following databases were searched for conference proceedings: Web of Knowledge, ZETOC. The following periodontal journals were hand searched: *Annals of Periodontology* (1996 to 2003), *Periodontology* 2000 (1993 to 2003). The following databases were searched for ongoing trials: US National Institutes of Health Trials Registry (http://clinicaltrials.gov), WHO Clinical Trials Registry Platform for ongoing trials. Reference lists of identified studies were also screened, as were reference lists of known papers on the topic.
4. Was the status of publication (ie, gray literature) used as an inclusion criterion?	**No.** Conference proceedings were searched through Web of Science and ZETOC. There were no language restrictions.
5. Was a list of studies (included and excluded) provided?	**Yes.** Lists of both included and excluded studies were provided.
6. Were the characteristics of the included studies provided?	**Yes.** A table describing the characteristics of included studies was provided.
7. Was the scientific quality of the included studies assessed and documented?	**Yes.** Risk of bias was assessed as described in the Cochrane Handbook for Systematic Reviews of Interventions.[12] Criteria evaluated were: random sequence generation, allocation concealment, blinding of participants, blinding of clinical operator, incomplete outcome data, selective outcome reporting, other biases.
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	**Yes.** The risk of bias assessment and level of evidence were used in formulating conclusions.
9. Were the methods used to combine the findings of studies appropriate?	**No.** Results were pooled for meta-analysis using a random-effects model since heterogeneity was evident. Combining data for comparison of nonsurgical periodontal treatment with no active intervention or usual care was appropriate, but combining data for comparison of SRP with SRP + antimicrobial is questionable because the type of antimicrobial, delivery mechanism, and mode of action varied considerably.
10. Was the likelihood of publication bias assessed?	**Yes.** Funnel plots, Begg and Mazumdar adjusted rank correlation test, and the Egger et al regression asymmetry test were used to evaluate publication bias. No publication bias was found.
11. Was the conflict of interest included?	**Yes.** Sources of support were disclosed, as were declarations of interest for all of the systematic review authors. Conflicts of interest of all included studies was part of the data extraction.

Fourteen of the included studies, with a total of 1,499 participants, compared SRP with no active intervention or usual care. Usual care was not specifically defined, but examples included supragingival prophylaxis, stand-alone oral hygiene instruction, and education or support sessions to improve self-help or self-awareness of oral hygiene. This evidence was judged by the authors to be of low quality. Mean HbA1C was reduced by 0.29 percentage points (95% CI: 0.48% to 0.10% lower) at 3 to 4 months, and 0.02 percentage points (95% CI 0.20% lower to 0.16% higher) at 6 months. Twenty-one studies with a total of 920 participants included head-to-head comparisons between different periodontal therapies. Overall, the quality of evidence was judged to be very low and no clear evidence of benefit from one treatment over another was provided. The only comparison that had sufficient data to conduct a meta-analysis was the comparison between SRP and SRP + antimicrobial (12 studies, 450 participants). The addition of antimicrobial therapy did not provide added benefit to SRP alone, with 0.00 percentage points change in HbA1c at 3 to 4 months (95% CI: 0.22% lower to 0.22% higher) and 0.04 percentage points lower HbA1c at 6 months (95% CI: 0.41% lower to 0.32% higher).

No studies that compared surgical with nonsurgical periodontal therapy met the inclusion criteria. There was insufficient evidence to make conclusions about the potential harm of any of the treatments, and patient-reported outcomes, cost implications, or diabetic complications were not reported in any of the studies.

Periodontal improvements were shown for all periodontal indices (BOP, CAL, GI, PI, and PPD) at 3 to 4 and 6 months when comparing periodontal therapy with no active intervention, usual care, or placebo. However, clear periodontal benefits of one treatment over another were not evident in the head-to-head comparisons between different periodontal therapies.

No publication bias was detected.

Conclusion

The systematic review authors conclude that SRP does improve glycemic control in people with diabetes, with 0.29 percentage points mean change in HbA1c at 3 to 4 months, but this may not be maintained after 4 months. There was no evidence to demonstrate benefit of one periodontal therapy over another in improving glycemic control.

Critical appraisal

The AMSTAR[14] criteria were used to critically appraise this systematic review (Table 1). Overall, this was a well-conducted systematic review. The authors developed a protocol a priori. A very comprehensive literature search was conducted that included seven databases of published studies, two databases of conference proceedings, and two databases of ongoing trials. Hand searching was performed for two periodontal journals, reference lists of included studies, and reference lists of known papers on the topic. There were no language restrictions. Study selection, data extraction, and risk of bias assessment were done in duplicate, with disagreements resolved by a third person. A list of included studies with study characteristics and a list of excluded studies were provided. Risk of bias was assessed. Pooling of data for the evaluation of nonsurgical periodontal treatment compared with no active intervention, usual care, or placebo was appropriate due to limited clinical heterogeneity (the studies were similar enough to each other that pooling the results for meta-analysis was appropriate). However, for the comparison between SRP and SRP + antimicrobial, the type of antimicrobial, delivery mechanism, and mode of action varied considerably, bringing into question whether it was appropriate to combine these studies for the meta-analysis. Publication bias was assessed, and conflicts of interest were disclosed for both the systematic review authors and authors of the included studies.

The quantity of evidence, 35 RCTs with 2,565 patients, was reasonable. Although RCTs are considered the highest level of experimental evidence, 29 of these studies were judged to be at high risk of bias, and the overall quality of the evidence was judged to be low or very low.

The clinical question pertained to both type 1 and type 2 diabetes. However, 33 of the 35 included studies investigated glycemic control only in patients with type 2 diabetes, and only two of the studies addressed patients with type 1 diabetes. Among the included studies, both the criteria to diagnose and measure type 1 or type 2 diabetes and the criteria to diagnose and measure periodontal disease varied. In addition, for some of the included studies medical management of diabetes changed during the course of the study and could have impacted the study results.

Although the authors intended to evaluate both surgical and nonsurgical periodontal therapy, only studies that evaluated nonsurgical periodontal therapy, mostly SRP, were identified. From the studies included in this systematic review, there is no evidence on the impact of surgical therapy on glycemic control.

Among the treatment modalities identified in the head-to-head comparisons were SRP, alternative mechanical therapy, alternative SRP, antimicrobial alone, SRP + single antimicrobial, SRP + multiple antimicrobials, SRP + statin, and SRP + bone modifier. There was insufficient evidence to conduct a meta-analysis for most of the head-to-head comparisons, with the exception of SRP versus SRP + antimicrobial. The authors report the summary estimate and CI of this head-to-head comparison; however, the corresponding forest plot used to calculate this summary estimate is not provided. In addition, there was considerable clinical heterogeneity in that the antimicrobial comparisons used a variety of different antimicrobial strategies with different delivery mechanisms and mechanisms of action (Table 2). Six studies evaluated systemic antimicrobials (doxycycline, mentronidazole, or amoxicillin), two evaluated sub-antimicrobial doxycycline (which inhibits mammalian

TABLE 2 Antimicrobials used in studies for comparison of SRP + antimicrobials with SRP alone

Study	Antimicrobial
Systemic antibiotic	
Al-Zahrani et al[15] (2009)	Systemic doxycycline (100 mg twice daily on day 1, then 100 mg daily for 13 days)
O'Connell et al[16] (2008)	Systemic doxycycline (200 mg 1 day prior to SRP, then 100 mg daily for 14 days)
Singh et al[17] (2008)	Systemic doxycycline (200 mg on treatment day, followed by 100 mg per day [p/d] × 14 days)
Tsalikis et al[18] (2014)	Systemic doxycycline (21 days total: 200 mg loading dose, followed by 100 mg daily for further 20 days)
Miranda et al[19] (2014)	Metronidazole (3 × 400 mg p/d for 14 days) and amoxicillin (3 × 500 mg p/d for 14 days) administered immediately after first SRP session
Rodrigues et al[20] (2003)	Systemic amoxicillin/clavulanic acid (given 24 hours prior to SRP, 875 mg twice daily for 14 days)
Subantimicrobial doxycycline	
DPTT Study Group et al[21] (2011)	Subantimicrobial doxycycline (20 mg twice daily for 3 months)
Gilowski et al[22] (2012)	Subantimicrobial-dose doxycycline (20 mg twice daily for 3 months)
Topical antimicrobial	
Haerian-Ardakani et al[23] (2014)	Topically applied tetracycline gel (5%)
Oates 2010[24]	Molecular free iodine antibacterial rinse, 15 mL twice daily for 90 days
Santos et al[25] (2013)	Full-mouth disinfection with chlorhexidine digluconate (CHX) 0.12% rinse for 60 days, and CHX gel (1%, applied to irrigate all treated pockets three times within 10 minutes)
Skaleric et al[26] (2004)	Minocycline hydrochloride microspheres (1 mg; controlled release bioresorbable polymer, at baseline and 12 weeks; in pockets ≥ 5 mm)

collagenase activity and does not function as an antibiotic[27,28]), and four studies evaluated topical antimicrobial (tetracycline gel, chlorhexidine rinse, iodine rinse, or minocycline microspheres). Given the different mechanisms of action for these variable antimicrobial strategies, it is questionable whether it was appropriate to combine these studies for the meta-analysis. The evidence was of low quality and thus provided no clear evidence of benefit from among these various treatment options.

Clinical implications

Overall, this was a well-conducted systematic review, with the only exception being the pooling of data for the comparison between SRP and SRP + antimicrobial, which was questionable due to clinical heterogeneity (differing antimicrobial therapies). However, the evidence available is of low quality. The preponderance of the evidence comes from patients with type 2 diabetes, bringing into question the validity of extrapolating these results to patients with type 1 diabetes. Furthermore, there are methodologic issues, such as the difference in diagnosis and evaluation of both diabetes and periodontal disease among the included studies, as well as changes in diabetes management in some of the studies during the time of the investigations, both of which could have impacted study results. The included studies were short-term and did not specifically provide any self-care instructions. Long-term management of periodontal disease, including a daily self-care routine, is needed to maintain the benefits of SRP, and possibly glycemic control. Because of these concerns, and the low quality of evidence as assessed by the authors, the results of this systematic review should be interpreted with caution.

The magnitude of the effect of SRP on glycemic control was mean reduction of HbA1c by 0.29 percentage points (95% CI: 0.48% to 0.10% lower) at 3 to 4 months and 0.02 percentage points (95% CI: 0.20% lower to 0.16% higher) at 6 months. The magnitude of effect is unclear, as medications used to manage diabetes typically result in 0.5 to 2 percentage points reduction in HbA1c.[29] Furthermore, the minor effect was not sustained to 6 months posttreatment, indicating any possible effect is transient. There was no evidence collected beyond 6 months posttreatment.

A recent systematic review and evidence-based guideline developed by the American Dental Association (ADA) evaluated nonsurgical treatment of

chronic periodontal disease with and without adjuncts such as antimicrobials.[30,31] They found moderate evidence for SRP in treating chronic periodontitis, as well as evidence supporting subantimicrobial-dose doxycycline, systemic antimicrobials, and minocycline microspheres, with differing levels of evidence supporting each of these modalities. Although this systematic review and guideline did not target patients with diabetes and evaluate the impact on glycemic control, they do provide evidence that SRP is effective in managing periodontal disease as well as evidence on which adjuncts to SRP are likely to be most effective in managing periodontal conditions.

There are many sources of evidence suggesting correlations between periodontal disease and systemic conditions, and the correlation is likely strongest between periodontal disease and diabetes and glycemic control. However, correlation does not imply causality, and therefore the impact of periodontal treatment on glycemic control remains uncertain. Moreover, a recent RCT[32] reported that nonsurgical periodontal therapy did not improve glycemic control in patients with type 2 diabetes and moderate to advanced chronic periodontitis. However, others have noted significant flaws in that study.[33] Given the weakness of the available evidence identified by this systematic review, and the minor magnitude of the effect, more certainty on the topic has not been gleaned. However, it is prudent to manage periodontal disease in all patients, especially those with risk factors. The results of this systematic review, along with the recent ADA systematic review and guideline,[30,31] suggest that SRP is an effective management strategy for periodontal disease. Furthermore, the ADA guideline indicates that use of subantimicrobial-dose doxycycline, systemic antimicrobials, and minocycline microspheres as adjuncts to SRP may improve periodontal outcomes. The effect of these adjuncts on glycemic control remains uncertain.

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