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Effects of Periodontal Therapy on Metabolic Control in Patients With Type 2 Diabetes Mellitus and Periodontal Disease

A Meta-Analysis

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Abstract: Epidemiologic studies have reported increased incidence, prevalence and acuity of periodontitis in adults with diabetes and some have also suggested that treating periodontal disease may improve glycemic control in diabetic patients.

This meta-analysis was conducted to evaluate the effects of different periodontal therapies on metabolic control in patients with type 2 diabetes mellitus (T2DM) and periodontal disease.

We searched the Medline, EMBASE and Cochrane Library (Central) databases up to January 2014 for relevant studies pertaining to periodontal treatments and glycemic control in adults with T2DM. The search terms were periodontal treatment/periodontal therapy, diabetes/diabetes mellitus, periodontitis/periodontal and glycemic control. The primary outcome measure taken from the included studies was glycated hemoglobin (HbA1c).

We compared differences in patients' pre- and post-intervention HbA1c results between a treatment group receiving scaling and root planing (SRP) combined with administration of oral doxycycline (n = 71) and controls receiving SRP alone or SRP plus placebo (n = 72). Meta-analysis was performed using Comprehensive Meta Analysis software.

Nineteen randomized controlled trials (RCTs) were identified. Four trials involving a total of 143 patients with T2DM and periodontal disease were determined to be eligible for analysis. Data of 1 study were not retained for meta-analysis because HbA1c results were recorded as median with IQR. Meta-analysis of the included 3 studies revealed no significant differences in HbA1c results between the periodontal treatment group (n = 71) and control group (n = 72) (HbA1c SMD = −0.238, 95% CI = −0.616 to 0.140; $P = 0.217$).

Systemic doxycycline added to SRP does not significantly improve metabolic control in patients with T2DM and chronic periodontitis. Current evidence is insufficient to support a significant association between periodontal therapy and metabolic control in this patient population. However, evidence suggests that periodontal therapy itself improves metabolic control and reinforces that T2DM is a risk factor for periodontitis.

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Abbreviations: HbA1c = glycated hemoglobin, PD = periodontal disease, RCT = randomized controlled trial, SMD = standardized mean difference, SRP = scaling and root planing, T2DM = type 2 diabetes mellitus.

INTRODUCTION

Periodontal disease (PD) is a chronic inflammatory disease that destroys the gingiva or tooth-supporting tissues. It is one of the most prevalent chronic infections in adults between ages 30 and 90 years in the United States and the most prevalent dental disease in people with diabetes, affecting up to 22% of diabetic patients.[1] PD is reported to affect about 90% of people globally.[2] The 2 major forms of PD, gingivitis and periodontitis, are the result of bacterial plaque, which ultimately destroys gingival tissue and periodontal attachment apparatus.[3] Although tooth-adherent microorganisms initiate PD, the individual inflammatory response along with concomitant chronic disease such as cardiovascular disease, chronic pulmonary disorders and diabetes, is responsible for the chronic nature of the disease and eventual breakdown of tissue. These conditions suggest that type 2 diabetes mellitus (T2DM) is a risk factor for periodontitis.[1] Epidemiologic studies over the years have consistently reported that increased incidence, prevalence and acuity of periodontitis is found among adults with T2DM.[4] Incidence of periodontitis increases as diabetic patients age and is both more frequent and more severe in T2DM patients with advanced systemic complications.[5]

Studies of diabetes patients with PD have examined different treatments for gingivitis and periodontitis that are targeted toward reducing oral bacteria and associated calculus. Patients with gingivitis without concomitant disease that influences oral health, may respond well to simply improving personal plaque control using a mix of mechanical and hygienic processes.[6] However, self-treatment alone is inconsistent and seldom results in maintaining plaque-free status, so professional reinforcement is usually advised.[6] Treatment of periodontitis is directed toward removing pathogenic bacteria and preventing recolonization; correcting modifiable risk factors such as smoking, alcohol abuse, medications or stress; and controlling systemic conditions such as autoimmune disease, diabetes mellitus, cardiovascular disease, lung disease, and osteoporosis.[7] Standard nonsurgical treatment for PD includes scaling and root planing (SRP), thorough removal

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of calculus and debris from tooth surfaces and gingiva, and adjunctive therapy such as laser treatment.[8] Adjunctive treatment also may include local or systemic antimicrobial administration,[9] and improving inflammatory host response via non-steroidal anti-inflammatory agents or biophosphonates.[7]

Although many studies have demonstrated associations between T2DM and PD, fewer studies have addressed whether effective treatment of periodontal disease effectively improves glycemic control. Some studies have shown that treating periodontal conditions results in improved metabolic control.[10–12] The results of previously published meta-analyses[13] and randomized controlled trials (RCTs)[14,15] also suggest that periodontal treatment can improve glycemic control in T2DM patients. Nevertheless, although nonsurgical treatment of periodontitis may improve periodontal and inflammatory status in diabetic patients, strong evidence is lacking to support improved glycemic control.[16] Current evidence is conflicting and appears to be insufficient to make clinical recommendations with confidence. Therefore, the purpose of the present meta-analysis was to evaluate the reported effects of periodontal therapies on metabolic control in T2DM patients with PD.

METHODS

Literature Search

The Medline, EMBASE and Cochrane Library (CENTRAL) databases were searched up to January 2014 using the following search terms: periodontal treatment/periodontal therapy, diabetes/diabetes mellitus, periodontitis/periodontal, and glycemic control. Reference lists of the relevant studies were searched manually. Titles and abstracts were screened for all studies and full-text was then obtained for those that met the inclusion criteria (below).

Study Selection

Studies that met the following criteria were included: an original investigation excluding review articles and meta-analyses; published RCT only; study subjects with T2DM and PD; comparison of different periodontal therapies; and studies providing comparable numerical results for glycated hemoglobin (HbA1c) measurement. Case reports, letters to the editor, systematic reviews and commentaries were excluded.

We initially identified RCTs that had investigated periodontal treatments and glycemic control in adults with T2DM. The primary outcome measure in the included studies was HbA1c, and differences between pre- and post-intervention HbA1c were compared in a treatment group and controls in all studies. Two author-reviewers independently determined the eligibility of all retrieved studies and uncertainties were resolved through discussion or by consultation with a third author-reviewer. The internal review board of National Yang Ming University reviewed and approved the study protocol for this meta-analysis.

Data Extraction and Quality Assessment of Included Studies

Data were extracted by two author-reviewers, including first author's name, year of publication, study design, treatments/interventions, number of participants in each group; and participants' ages and gender, periodontal disease index, follow-up period and HbA1c as primary outcome. The methodological quality of each study was assessed using the risk-of-bias assessment tool outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0.).[17] Two author-reviewers subjectively reviewed all studies and assigned a value of ''low risk,'' ''high risk,'' or ''unclear'' to the following aspects: (a) random sequence generation; (b) allocation concealment; (c) blinding function (patients, personnel, and assessors); (d) adequate assessment of each outcome; (e) avoidance of selective outcome reporting; and (f) whether or not intention-to-treat analysis was included.

Primary Outcome Measure

The main outcome measure is the differences in patients' HbA1c values between pre- (baseline) and post-treatment/intervention (at final visit) in the included studies.

Statistical Analysis

Differences in patients' HbA1c values from baseline to final visit were compared between participants receiving treatment (treatment group) vs those receiving standard control therapies (control group). An χ^2-based test of homogeneity was performed and the Q and inconsistency index (I^2) statistics were determined. If I^2 was $>50\%$ or $>75\%$, the trials were considered to be heterogeneous or highly heterogeneous, respectively. If I^2 was $<25\%$, the studies were considered to be homogeneous. If the I^2 statistic ($>50\%$) indicated that heterogeneity existed between studies, a random-effects model (DerSimonian–Laird method) was performed. Otherwise, fixed-effects models (Mantel–Haenszel method) were performed. For each outcome measure, standardized mean difference (SMD) with corresponding 95% confidence intervals (CIs: lower and upper limits) were calculated for each individual study and for the studies combined. A two-sided P-value <0.05 was established as statistical significance when comparing groups. Sensitivity analysis of the outcomes was performed using the leave-one-out approach. Due to the small number of selected studies, assessing for publication bias using funnel plot was considered inappropriate.[18] All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Literature Search

Detailed search procedures are summarized in Figure 1. The database search identified 19 studies, of which 4 met the inclusion criteria and were potentially eligible for analysis.[19–22] Fifteen studies were excluded[10,12,14–16,23–32] based on lack of treatment intervention,[7] an untreated control group,[5] and no numerical results data.[1] The full text of the 4 potentially eligible studies met all inclusion criteria and these studies were determined to be eligible for inclusion in the meta-analysis (Figure 1).

Baseline Characteristics of Selected Studies

Characteristics of the 4 included studies are summarized in Table 1. Enrolled subjects in the 4 RCTs included a total of 143 patients with T2DM and PD; periodontitis was described as ''chronic'' or ''severe chronic'' in the included studies. Participants' ages were similar among all studies and between therapies; gender distribution varied between studies and between treatment and control groups in individual studies. Overall, 71 patients received SRP combined with administration of oral doxycycline (treatment group), while 72 participants received SRP alone or SRP plus placebo (control group) (Table 1).

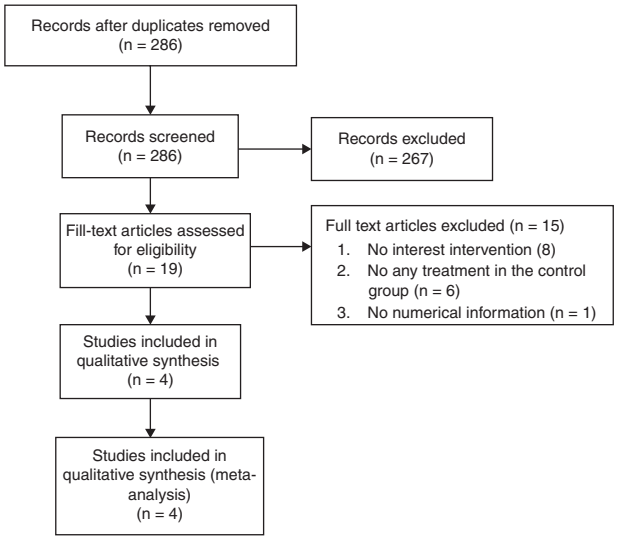

FIGURE 1. Flow chart of literature search and study selection.

Quality Assessment of Included Studies

The risk of bias in the included studies is summarized in Figure 2A and an overall assessment of risk of bias is presented in Figure 2B. Assessment of the studies by independent reviewers revealed the following: (a) random sequence generation was appropriate in all 4 studies; (b) allocation concealment was appropriate in 3 studies;[19–21] (c) only 1 study reported personnel, participants and assessor blinded to treatment,[20] (d) all studies were judged to be at low risk of attrition bias; (e) 2 studies did not have reporting bias,[20,22] and (f) intention-to-treat analysis was not included in any of the 4 studies.

Study Outcomes

The primary outcomes are the HbA1c results of patients in the included studies, which are summarized in Table 2. Data of 1 study[20] were not retained for meta-analysis because HbA1c results were recorded as median with IQR.

HbA1c SMD Forest Plot

Figure 3 shows the Forest plot for the SMD of the primary outcome HbA1c between patients in the treatment group and those in the control group. A fixed-effect analysis was applied because there was no evidence of heterogeneity among the studies (Q-statistic = 1.093, $I^2 = 0\%$, $P = 0.579$). Meta-analysis of the included 3 studies revealed no significant differences in HbA1c results between all patients in the periodontal treatment group (n = 71) and control group (n = 72) (HbA1c SMD = −0.238, 95% CI = −0.616 to 0.140; $P = 0.217$) (Figure 3).

Sensitivity Analysis

Figure 4 shows the Forrest plot for the SMD of HbA1c with individual studies evaluated separately among the treatment group and the control group. The direction and magnitude did not change with the exclusion of individual studies, indicating good reliability of the meta-analysis (Figure 4).

DISCUSSION

In the present meta-analysis, among the 19 RCTs identified initially, only 4 with a total of 143 patients with T2DM and PD were determined to be eligible for analysis. Data of 15 studies were excluded and data of 1 study were excluded from meta-analysis because HbA1c results were shown as median with IQR. Meta-analysis of the remaining 3 studies revealed no significant differences in HbA1c results between the periodontal treatment group and control group, which does not appear to support an association between periodontal therapy with doxycycline and metabolic control in T2DM patients with periodontal disease even though HbA1c levels decreased somewhat in both groups.

A study conducted in China demonstrated that non-surgical therapy for periodontitis was beneficial in both maintaining periodontal health and reducing blood glucose levels in patients with T2DM and chronic PD.[10] The treatment group in that study received doxycycline and SRP as in the present study, resulting in significantly reduced plaque index and bleeding on probing scores and improved HbA1c results compared to controls. Stewart et al[12] also found that periodontal treatment for 9 months had a 17.1% improvement in glucose levels compared to those of controls. Another study found that inflammatory cytokine levels decreased and adiponectin levels increased in patients with moderately or poorly controlled T2DM.[32] Our study focused on the differences in pre- and post-intervention HbA1c results as a measure of glycemic control, while other studies relied on outcomes of plaque index, probing scores, glucose levels and other glycemic parameters.

It must be remembered when comparing studies that HbA1c results monitor overall glycemic control achieved within the previous 2 to 3 months and the intervals between tests must be at least 2 months to be able to note relevant differences or changes between pre- and post-intervention.[16] This was considered in each of the 4 studies selected for analysis and all authors had included appropriate intervals in follow-up times. However, in the interpretation of HbA1c results, SMDs are especially important as a uniform scale applicable in meta-analysis when methodological differences in HbA1c measurement are noted between studies. For example, although 1 study was excluded from meta-analysis in the present study because HbA1c results were shown as median with IQR, the HbA1c SMD of the included studies was −0.238 (95% CI = −0.616 to 0.140; $P = 0.217$). One meta-analysis by Teeuw et al[33] demonstrated a weighted mean difference in HbA1c for pre- and post-intervention of 0.40 (95% CI 0.77 to −0.04%, $P = 0.03$), which favored periodontal intervention in patients with T2DM. However, this improvement in HbA1c must be interpreted carefully due to limited robustness as evidenced by heterogeneity among studies selected for meta-analysis. Darré et al[34] reported an SMD of 0.46 (95% CI 0.11 to 0.82), indicating a significant reduction in HbA1c post-treatment. The meta-analysis by Janket et al[13] reported a weighted average decrease of 0.38% in actual HbA1c levels of all included studies, 0.66% when restricted to patients with T2DM and 0.71% when patients also received antibiotic treatment. However, differences in pre- and post-intervention HbA1c results were not significant.

A previous meta-analysis of intervention studies that focused on the effects of periodontal treatment on glycemic control in T2DM patients suggested that successful management of periodontal infection leads to both reductions in local symptoms of the disease and improved control of glucose metabolism. However, in that meta-analysis, post-intervention results were not significantly different from baseline results.[13] In the RCT conducted by Singh et al,[14] 2 treatment groups were employed, 1 receiving systemic doxycycline plus SRP and 1 receiving SRP alone, and effects of periodontal treatment

TABLE 1. Baseline Characteristics of the Included Studies

Study no.	First author (year)	Type of study	Type of patients	Periodontal therapy		Baseline characteristics			Periodontal disease index		
				Therapy by group	Description of therapies	N of patients	Age (years)	Males n (%)	Probing depth (mm)	Clinical attachment level (mm)	Follow-up (months)
1	Gaikwad[19]	RCT	Type 2 DM + Generalized chronic periodontitis	Treatment group	SRP + doxycycline (100 mg/day for 15 days)	25	30–70	16 (64)	3.36 ± 0.35	3.62 ± 0.50	4
				Control group	SRP	25		18 (72)	3.34 ± 0.40	3.46 ± 0.56	
2	Gilowski[20]	RCT	Type 2 DM + Chronic periodontitis	Treatment group	SRP + doxycycline (20 mg bid for 3 months)	17	57.6 ± 8.0	10 (59)	2.9 (2.5, 3.7)*	3.8 (3.2, 5.0)	3
				Control group	SPR + Placebo (saccharumlacti)	17	56.0 ± 9.0	8 (47)	2.9 (2.7, 3.1)*	4.2 (3.5, 5.1)*	
3	Al-Zahrani[21]	RCT	Type 2 DM + Moderate-to-severe chronic periodontitis	Treatment group	SRP + doxycycline (100 mg bid for day 1 and then 100 mg/day for 13 days)	14	51.4 ± 6.2	4 (29)	3.26 ± 0.45	3.9 ± 0.74	n/a
				Control group	SRP	15	53.1 ± 10.9	7 (47)	3.24 ± 0.66	4.66 ± 1.32	
4	O'Connell[22]	RCT	Type 2 DM + Periodontitis	Treatment group	SRP + doxycycline (initial dose of 200 mg and 100 mg/day for 2 weeks	15	52.3 ± 6.3	8 (53)	3.0 ± 0.5	10.7 ± 1.6	3
				Control group	SRP	15	53.5 ± 13.6	6 (40)	2.9 ± 0.8	10.2 ± 1.30	

N/a = not available, T2DM = type 2 diabetes mellitus, RCT = randomized controlled trial, SRP = scaling and root planing.
* Median (IQR: Q1, Q3).

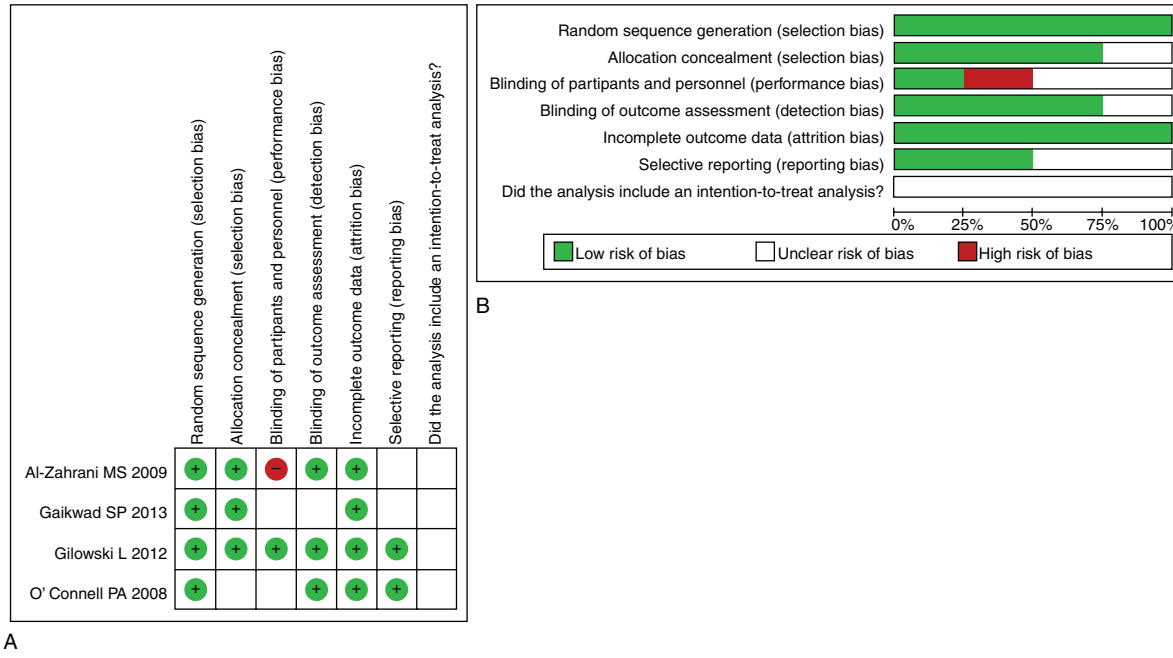

FIGURE 2. Assessment of risk of bias. (A) Summary of risk assessment of bias (B) Overall risk assessment of bias.

on metabolic control in diabetes patients were evaluated. Those investigators found a statistically significant improvement in glycemic control in the group receiving periodontal treatment combined with the antibacterial effects of doxycycline, which was demonstrated by improved periodontal results and reduced HbA1c results; however, the decreases in fasting blood glucose and 2-hour post-prandial blood glucose levels were not significant. Systemic doxycycline inhibits metalloproteinase activity and also has antimicrobial effects beneficial to controlling periodontal inflammation. With these special advantages of docycycline, it is not surprising that the combination therapy in the treatment group in our study had measureable clinical effects compared to the control group, and had noticeable but non-significant effects in other studies.[10,12] Among our included studies, anti-infective and systemic doxycycline periodontal therapy was shown to influence patients' systemic conditions favorably even though statistically significant differences were not observed. However, 1 study suggested that the noted improvements in glycemic control and reduced inflammatory markers could just as easily have been the result of diet,[22] and yet diet was not controlled in that study nor evaluated in any of the included studies. Previous systematic reviews and meta-analyses have suggested that periodontal therapy has a positive effect on glycemic control in patients with T2DM.[13,17,33,34] Results of a recent meta-analysis by Sgolastra et al[35] indicated that SRP significantly reduced HbA1c in the diabetic dental patients of 5 RCTs, which supports the effectiveness of SRP alone in improving glycemic control in T2DM patients with chronic PD. In the present study, it appears that even in the absence of significant differences between groups with and without doxycycline therapy, the measurable clinical effects are definitely signs of improved metabolic control, and the lack of significant between-group differences primarily suggests that periodontal therapy itself is able to improve metabolic control.

Limitations

Results of this study are limited by the small number of studies analyzed and the related small number of subjects. In this meta-analysis, the lack of significant differences in HbA1c results between all patients in the periodontal treatment group (n = 71) and control group (n = 72) suggests that evidence in the

TABLE 2. Differences in Subjects' HbA1c Results at Baseline and Final Visit by Study

Study no.	First author (year)	HbA1c (%)	
		Control groups (before to after)	Treatment groups (before to after)
1	Gaikwad[19]	8.38 ± 0.89 to 7.00 ± 0.76	8.06 ± 1.1 to 7.11 ± 0.99
2	Gilowski[20] *	6.7 (6.3, 7.0) to 6.7 (6.3–7.7)	6.2 (6.0, 7.8) to 6.3 (5.5–7.3)
3	Al-Zahrani[21]	8.42 ± 1.65 to 7.71 ± 1.77	8.75 ± 1.43 to 8.22 ± 0.95
4	O'Connell[22]	11.8 ± 1.6 to 10.30 ± 2.30	10.7 ± 2.0 to 9.80 ± 2.00

HbA1c = glycated hemoglobin.
* Gilowski (2012) study was represented as median (IQR: Q1, Q3).

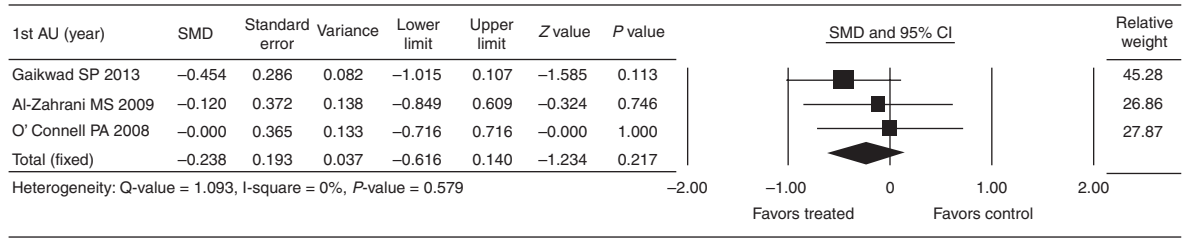

FIGURE 3. Forrest plot comparing before/after HbA1c in treated subjects vs control subjects by study. CI = confidence interval, Lower limit = lower bound of 95% CI, SMD = standardized mean difference, Upper limit = upper bound of 95% CI, 1st AU = first author.

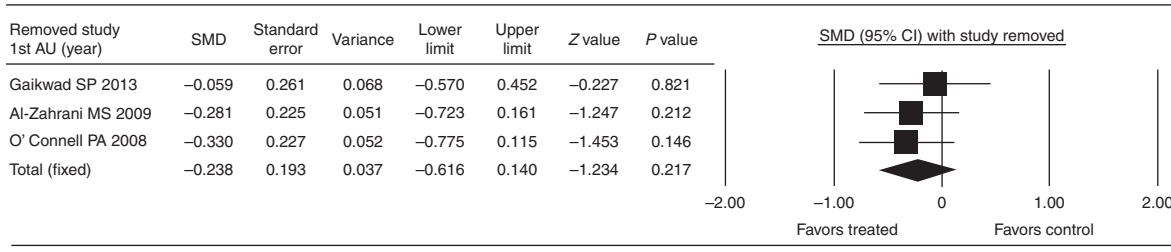

FIGURE 4. Sensitivity analysis of the influence of each study on pooled estimates of HbA1c. The leave-one-out approach was used. CI = confidence interval, Lower limit = lower bound of 95% CI, Upper limit = upper bound of 95% CI, SMD = standardized mean difference, 1st AU = first author.

small number of included studies may be insufficient to demonstrate significant differences between the SRP + doxycycline treatment in the treatment group vs that of SRP and placebo in the controls. Typically, a meta-analysis is conducted because of the advantage of having greater statistical power and its value as an evidence-based resource able to extrapolate confirmatory data analysis across the affected population. However, the lack of sufficient evidence in the present meta-analysis may not contribute to making clinical recommendations with confidence. More RCTs with larger cohorts and longer-term treatment are still needed to evaluate variables of periodontal disease and glycemic control and to investigate associations between periodontal therapy and metabolic control in T2DM patients with PD.

CONCLUSIONS

In conclusion, adding doxycycline to periodontal therapy with SRP does not significantly improve metabolic control in patients with T2DM and chronic periodontitis. Currently, available evidence is insufficient to support a significant association between periodontal therapy and metabolic control in T2DM patients with PD, however, evidence suggests that periodontal therapy itself improves metabolic control. Results also reinforce that diabetes is a risk factor for periodontitis. More and larger RCTs are needed before findings of metabolic control in T2DM patients with PD can be generalized to other patients with diabetes.

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