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Review article

Systemic antibiotics adjuvants to scaling and root planing in type 2 diabetic and periodontitis individuals: Systematic review with network meta-analysis

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ABSTRACT

Targeting inflammatory pathways is considered a common strategy to control type 2 diabetes (T2D) and periodontitis. This overview was to validate systemic antibiotics as an adjuvant to scaling and root planing (SRP) for the treatments of periodontal patients with T2D. Literature searches were conducted using Web of Science, PubMed, Cochrane, and EMBASE. Randomized trials comparing SRP and systemic antibiotics on glycated hemoglobin (HbA1c) and probing pocket depth (PPD) in adults with T2D and periodontitis were analyzed using network meta-analysis and meta-regression. At 3-month postintervention, meta-analyses of 16 studies revealed that SRP and SRP plus systemic antibiotics (SRPa) had similar significant effects in reducing HbA1c levels of − 0.72% and − 0.96% respectively. While SRP and SRPa also, respectively, reduced PPD of − 0.67 and − 0.89 mm, SRPa showed a better reduction than SRP. At 6-month postintervention, meta-analyses of 7 trials revealed that only SRP was effective in reducing HbA1c levels (−0.29%) but not SRPa. Although both SRP and SRPa still significantly reduced PPD by − 0.56 and − 0.81 mm, respectively, there was no difference between them. The current overview suggested that routine SRP alone is highly recommended for patients with T2D and periodontitis, since systemic antibiotics as an adjuvant provide a rather short-term effect.

Contents

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1. Introduction

Type 2 diabetes (T2D) accounts for approximately 90–95% of all diagnosed cases of diabetes, which is the leading cause of kidney failure, lower-limb amputations, and adult blindness. T2D is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs. The common mechanism of T2D pathophysiology is chronic systemic inflammation [1]. Therefore, targeting cytokine production and secretion to prevent further activation of inflammation has been proposed with the intention of stopping the initiation and progression of T2D. Since glycated hemoglobin A1c (HbA1c) is the index measured as a diagnostic test for diabetes and as a clinical assessment of glycemic control [2]. Thus, how to effectively control systemic inflammation and reduce HbA1c levels is a critical issue.

Periodontitis is the most common chronic inflammatory disease of the oral cavity. It is caused by bacteria found in dental plaque that accumulate on tooth surfaces. Infection leads to the loss of supportive connective tissues and alveolar bones [3], which can be reflected in increased probing pocket depths (PPD), the main parameter for assessing periodontal destruction [4]. It is noteworthy that the responses induced by dental bacterial infection are not confined to the oral cavity but are also associated with systemic inflammation [5]. The bacteria products released by periodontal pathogens and inflammatory mediators generated during periodontal inflammation could lead to systemic inflammation [6]. The elevated systemic inflammatory burden in people with periodontitis increases the risks of chronic diseases, which therefore has a negative impact on glycemic control of diabetic patients. Furthermore, the pathophysiology shared by periodontitis and T2D is likely also driving changes in proinflammatory cytokines and overall inflammatory burdens in patients with either disease [7,8]. The overacting inflammation in periodontitis may also increase the risks of T2D. Thus, preventing periodontal inflammation is regarded as an important strategy for controlling glycemic conditions and reducing T2D-realted complications [8].

Periodontal diseases are commonly treated either by surgical intervention or non-surgical periodontal therapy (NSPT). Scaling and root planning (SRP) is the fundamental NSPT, which effectively reduces or eliminates bacteria in subgingival plaque by disrupting dental biofilms by mechanical instrumentation [9]. In patients with T2D and periodontitis, only SRP had shown significant improvements in plasma levels of tumor necrosis factor alpha (TNF-α) and HbA1c [10]. It is assumed that SRP not only reduced periodontal inflammation, but also decreased systemic inflammation, and therefore HbA1c improved.

On the other hand, systemic antibiotics are often prescribed to patients to control acute inflammatory. Therefore, thoroughly elucidating the role of systemic antibiotics in chronic inflammatory diseases, such as T2D and periodontitis, is an interesting issue. Systemic antimicrobials in conjunction with SRP have been reported to offer an additional benefit over SRP alone in patients with pure periodontitis, in terms of changes in PPD [11]. Further, systemic review studies showed that antibiotics improve the efficacy of SRP in reducing PPD in patients with T2D and periodontitis at 3-month follow-up [12–14]. However, their effects on HbA1c, the important therapeutic target in T2D patients, were not validated. An early meta-analysis showed that, compared to SRP alone, systemic antibiotics as an adjunct to SRP did not significantly improve HbA1c in patients with T2D and periodontitis [15]. However, the study only evaluated HbA1c and not PPD, which limited the exploration of the interaction between these two diseases when receiving different treatment modalities. Moreover, this meta-analysis only included three studies [16–18] and one of which was not a randomized controlled trial [16]. Despite the recent publication of several related studies, the effect of antibiotic as an adjuvant to SRP on simultaneous control of PPD and HbA1c remained controversial. Therefore, the aims of this meta-analysis were to assess whether systemic antibiotics as adjuvants to SRP could benefit periodontal patients with T2D and to reveal if different treatment modalities could provide a long-term effect in reducing HbA1c.

2. Materials and methods

The PICOS (participants, interventions, comparisons, outcomes, and study design) strategy was used to collect the appropriate papers to answer the question “Do systemic antibiotics as adjuvants to SRP have better treatment glycemic control effects in patients with T2D and periodontitis?”.

- Participants: adults with T2D and periodontitis;
- Interventions: scaling and root planing (SRP) or SRP plus systemic antibiotics (SRPa);
- Controls: no treatment, delay treatment, supragingival scaling, or oral hygiene instruction only;
- Comparisons: SRP vs. control, SRPa vs. control, and SRP vs. SRPa;

• Primary outcomes: the HbA1C level at the baseline, 3-month or 6-month post-intervention;

• Secondary outcomes: the mean periodontal probing depth (PPD) at baseline, 3-month or 6-month post-intervention.

2.1. Eligibility criteria

For this analysis, any randomized controlled trials (RCTs) published in English demonstrating the effect of SRP or SRPa on glycemic control were included. Studies that reported combined outcomes from both type 1 and type 2 diabetic patients were excluded, given the different pathogenesis of type 1 and type 2 diabetes.

2.2. Search strategy and study selection

We adhered to the PRISMA guidelines for reporting systematic reviews that incorporate network meta-analyses of health care interventions (Supplementary 1) [19]. Electronic databases (Web of Science, PubMed, Cochrane, and EMBASE) have been explored up to October 11, 2021. The MeSH terms used in the electronic searches were (((periodontal diseases) OR (periodontitis)) AND (diabetes mellitus, type 2)) AND (((dental scaling) OR (root planing)) OR (subgingival curettage)). The references of the included articles and relevant systematic reviews and meta-analyses were tracked for additional studies. There was no restriction in terms of language. To identify relevant articles, titles and abstracts of retrieved papers were independently screened by two reviewers (SYW, YHC) according to the eligibility criteria. The conflicts were resolved through discussion.

2.3. Data extraction

Following data were independently extracted by two authors (SYW, YHC) from each study: including the first author's last name, publication year, journal, participants' country, sex, age, BMI, sample size, duration of diabetes, and HbA1c and PPD at baseline, intervention types, and differences in the mean values of two time points or postintervention mean values with corresponding standard deviations (SDs). The authors of the included studies were not contacted for missing data or unclear information.

2.4. Methodological quality of included reviews

The methodological quality of the included papers was independently assessed by two investigators (SYW, YHC). The quality of each study was assessed using the Cochrane Collaboration RoB-2 tool [20]. RoB-2 is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct, and reporting. Based on the answers to the signaling questions, proposed judgement about the risk of bias arising from each domain, i.e. "Low" or "High" risk of bias, or "Some concerns", was generated by an algorithm.

2.5. Data syntheses and analyses

The changes from the baseline values of HbA1c or PPD to the postintervention ones of each intervention were taken as the measure of treatment efficacy. To compare the pooled relative effect of each intervention with every other intervention, the random-effects pairwise meta-analysis was performed with STATA (version 14.0; StataCorp LLC, College Station, Texas, USA). The heterogeneity between the trial results was tested using Cochrane's Q test and I^2 statistics. Then, frequentist arm-based network meta-analysis (NMA) was performed with the programming for language R (version 4.1.3) [21], to synthesize all available evidence to yield a clinically meaningful relative ranking of the different interventions. The summary standardized mean differences (SMD) with their 95% confidence intervals (95% CIs) were presented. Statistical significance was assessed by examining 95% CIs, where CIs of mean changes that did not include the value 0 were deemed statistically significant. Publication bias was assessed using visual exploration of funnel plots and the Egger's test. Meta-regressions were used to explore whether the intervention level or baseline HbA1c level characteristics explained heterogeneity in treatment effects.

3. Results

3.1. Search results

The search of the electronic database and manual searches identified 5252 studies. After the removal of duplicate studies, a total of 2590 studies were retained from the primary searches. After title and abstract selection, 29 publications were retained for full-text review. Twelve RCTs, which did not meet the inclusion criteria or had incomplete/unretrievable data, were excluded after full-text evaluation. The PRISMA diagram of the study selection process is shown in Supplementary 2. The remaining 17 studies [7,18,22–36] included in the NMA were summarized in Table 1, and the inclusion and exclusion criteria of each included studies were listed in Supplementary 3.

3.2. Characteristics of included studies

The included studies were published between 2003 and 2021, enrolling a total of 1448 patients with T2D and periodontitis. One study recruited more than 100 participants [7]. Eight groups received SRPa therapy [18,23,24,27,30–33]. Among these groups, doxycycline [27,36], amoxicillin and metronidazole [31] and amoxicillin/clavulanic acid [7] were used. Seventeen groups received SRP therapy [7,18,22,23,25–30,32–36], while 15 groups did not receive treatment. This meta-analysis pooled data from the included studies, which were conducted in Brazil (n = 86), India (n = 196), Saudi Arabia (n = 29), China (n = 207), Iran (n = 40), Greece (n = 66), the United States (n = 475), Japan (n = 37), sub-Saharan Africa (n = 30), Turkey (n = 44), Egypt (n = 88), and Pakistan (n = 150).

3.3. Quality assessment

Among the studies retrieved for this systematic review, 2 studies had a low risk of bias [27,33], while others [7,18,22–26,28–32,34–36] had some concerns (Table 2). The nature of periodontal interventions likely led to some difficulties in patient blinding, which was addressed in the study design of only three studies [24,27,33]. The lack of information about this issue caused some concerns about the overall risk of bias.

3.4. Three-month HbA1c and PPD changes

3.4.1. Pairwise meta-analysis

The pooled pre/post HbA1c and PPD changes from 16 studies [18,22–36] with 24 comparison groups enrolling 1261 participants were shown in Fig. 1. While SRP (SMD: −0.65%; 95% CI: −0.97/−0.32) or SRPa (SMD: −1.17%; 95% CI: −1.64/−0.71) reduced HbA1c compared to the control with significance (p = 0.000 and 0.011, respectively), SRPa did not reduce HbA1c more than SRP (SMD: −0.15%; 95% CI: −0.37/0.08). Meanwhile, SRP (SMD: −0.63 mm; 95% CI −0.78/−0.47) or SRPa (SMD: −1.04 mm; 95% CI −1.72/−0.36) also reduced PPD compared to the control with significance (both p = 0.000). No

Table 1
Characteristics of participants at baseline of interventions in included studies.

Author, Year, Journal Country, Source	No.	gender (M/F)	Age (y/o)	Duration of T2D (yrs; mean ± SD)	BMI (kg/m^2; mean ± SD)	baseline HbA1C (%)	baseline PPD (mm)	group	Interventions	follow up (mo)	Conclusions
Rodrigues et al., 2003. J Periodontol. Brazil, a university hospital	15	NR	NR	NR	NR	9.5 ± 2.4	2.7 ± 0.7	SRP + Anti	OHI, SRP in 2 sessions under LA within 24–36 hrs, Augmentin 1 g BID for 2 weeks	3	Periodontal therapy improved glycemic control in patients with T2D in both groups; however, the reduction in HbA1c reached statistical significance only in the group receiving SRP alone.
	15	NR	NR	NR	NR	8.8 ± 1.8	3.2 ± 0.8	SRP	OHI, SRP in 2 sessions under LA within 24–36 hrs		
Kiran et al., 2005. J Clin Peiorodontol. Turkey, a university hospital	22	46/54	55.95 ± 11.21	9.32 ± 8.36	NR	7.31 ± 0.74	2.29 ± 0.49	SRP	SRP + OHI	3	NSPT is associated with improved glycemic control in T2D patients.
	22	36/64	52.82 ± 12.27	8.05 ± 5.90	NR	7.00 ± 0.72	2.24 ± 0.70	no_tx	Delayed periodontal treatment for 3 months		
Singh et al., 2008. Int J Diabetes Dev Ctries. India, a dental collage and a hospital	15	NR	above 30	NR	NR	7.9 ± 0.7	2.67 ± 0.35	SRP	OHI, SRP under LA	3	NSPT is associated with improved glycemic control in T2D patients.
	15	NR	above 30	NR	NR	8.3 ± 0.7	2.52 ± 0.47	SRP + Anti	OHI, SRP under LA, Doxycycline 200 mg on first day and then 100 mg for 14 days		
	15	NR	above 30	NR	NR	8.08 ± 0.7	2.44 ± 0.26	no_tx	No treatment during the study		
Al-Zahrani et al., 2009. J Periodontol. Saudi Arabia, a university hospital	14	10/4	51.42 ± 6.24	NR	NR	8.42 ± 1.65	3.26 ± 0.45	SRP + Anti	OHI, SRP in 1–4 sessions under LA within 7 days, Doxycycline 200 mg for first day and 100 mg/day for 13 days	3	NSPT plus doxycycline showed an improvement in the glycemic control in T2D patients.
	15	8/7	53.14 ± 10.91	NR	NR	8.75 ± 1.44	3.24 ± 0.66	SRP	OHI, SRP in 1–4 sessions under LA within 7 days		
Chen et al., 2012. J Periodontol. China, a university	42	23/19	59.86 ± 9.48	8.69 ± 5.25	24.46 ± 2.82	7.31 ± 1.23	2.66 ± 0.68	SRP	SRP under LA at baseline and sub-G debridement at 3 mo F/U	3,6	NSPT can effectively improve periodontal and circulating inflammatory status.
	43	26/17	57.91 ± 11.35	6.93 ± 4.31	23.88 ± 3.56	7.29 ± 1.55	2.57 ± 0.66	SRP	SRP under LA at baseline and supra-G prophylaxis with no intervention in deep periodontal pocket at 3 mo F/U		
	41	17/24	63.2 ± 8.51	9.56 ± 6.02	23.51 ± 3.10	7.25 ± 1.49	2.47 ± 0.57	no_tx	No treatment during the study		
Moeintaghavi et al., 2012. Aust Dent J. Iran, a diabetics clinic and the Mashhad Diabetics Center	22	9 /13	NR	NR	NR	8.15 ± 1.18	2.31 ± 0.65	SRP	OHI, SRP	3	NSPT could improve metablic control in T2D patients.
	18	11/7	NR	NR	NR	8.72 ± 2.22	2.06 ± 0.24	no_tx	OHI		
Miranda et al., 2014. J Clin Periodontol. Brazil, a university	29	12/17	54.0 ± 8.2	8.0 ± 3.2	NR	8.53 ± 1.56	3.6 ± 0.5	SRP + Anti	OHI, extraction of teeth with advanced decay, provisional restoration and filling overhang removal, SRP in 4–6 sesstions under LA, Metronidazole 400 mg and Amoxicillin 500 mg TID for 14 days	3,6,12	The adjunctive use of Metronidaxole + Amoxicillin significantly improved the clinical and microbiological outcomes of SRP in the patients with T2D and periodontitis.
	27	18/9	53.7 ± 8.0	7.4 ± 3.6	NR	8.99 ± 1.63	3.6 ± 0.6	SRP	OHI, extraction of teeth with advanced decay, provisional restoration and filling overhang removal, SRP in 4–6 sesstions under LA, placebo for 14 days		
Tsalikis et al., 2014, J Clin Periodontol. Greece, a university and a hospital	31	18/13	62.9 ± 10	11.8 ± 5.9	NR	6.70 ± 0.61	3.01 ± 0.77	SRP + Anti	OHI, SRP, Doxycycline (200 mg loading and 100 mg for 20 days)	3,6	Adjunctive sustemic doxycycline dose not significantly enhance the effects of SRP in well-controlled T2D patients.
	35	20/15	57.94 ± 8.22	10.2 ± 5.7	NR	6.89 ± 0.60	3.03 ± 0.73	SRP	OHI, SRP, placebo (2 capsules 1st day and 1 capsule for 20 days)		

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Table 1 (*continued*)

Author, Year, Journal Country, Source	No.	gender (M/F)	Age (y/o)	Duration of T2D (yrs; mean ± SD)	BMI (kg/m^2; mean ± SD)	baseline HbA1C (%)	baseline PPD (mm)	group	Interventions	follow up (mo)	Conclusions
Wu et al., 2015. J Periodontol. China, a university and a hospital	21	12/11	54.09 ± 6.57	4.00 ± 1.76	22.22 ± 0.64	7.41 ± 0.20	3.73 ± 0.58	SRP	Sub-G SRP were completed within 1 mo of the first visit.	3,6	NSPT is helpful for glucose control.
	21	10/13	55.52 ± 5.22	4.22 ± 1.57	22.14 ± 0.72	7.39 ± 0.16	3.71 ± 0.61	no_tx	OHI		
Kaur et al., 2015. J Oral Sci. India, Post-graduate Institute of Dental Sciences	23	10/13	52.83 ± 5.04	8.76 ± 6.71	26.26 ± 3.82	6.03 ± 0.47	2.82 ± 0.44	SRP	SRP (good control)	3,6	NSPT improved glycemic control and periodontal thealth in patients with T2D. However, patients with poor baseline glycemic control has less clincial impreovement than did those without diabetes and those with good glycemic control.
	25	14/11	54.28 ± 5.93	6.40 ± 2.80	25.93 ± 3.99	5.94 ± 0.75	2.92 ± 0.58	no_tx	No treatment during the study (good control)		
	27	12/15	50.96 ± 6.43	8.41 ± 6.25	26.26 ± 3.99	9.99 ± 2.02	3.08 ± 0.45	SRP	SRP (poor control)		
	25	12/13	51.60 ± 5.93	7.70 ± 5.60	26.93 ± 3.62	9.81 ± 2.24	3.23 ± 0.48	no_tx	No treatment during the study (poor control)		
Geisinger et al., 2016. J Periodontol. USA, 5 academic medical centers	240	133/107	56.8 ± 10.6	12.5 ± 8.2	34.5 ± 7.2	7.84 ± 0.7	3.3 ± 0.6	SRP	SRP + SPT at 3 mo visit	6	NSPT and periodontal disease severity were not associated with significant changes in serum biomarkers. Correlations among changes in E-selectin, IL-6 and DM-related variables suggest that T2D may be the primary driver of systemic inflammation.
	235	122/113	58.1 ± 9.4	11.5 ± 8.6	34.2 ± 6.6	7.77 ± 0.6	3.3 ± 0.7	no_tx	Delayed periodontal treatment for 6 mo		
Wang et al., 2017. Braz. Oral Res. China, Community Health Center	19	12/7	61.58 ± 4.69	8.47 ± 3.08	24.32 ± 2.70	7.63 ± 0.89	3.66 ± 0.60	SRP	OHI, supra- and sub-G scaling, extraction hopless teeth, restoration of balanced occlusion	3	Periodontal therapy may relieve periodontal inflammation, which causes a reduction of insulin-anatagonizing adipokines and an increase in insulin-sensitizing adipokines, therby eliciting an improvement in glycemic control.
	20	14/6	61.90 ± 6.75	7.70 ± 4.69	23.72 ± 3.46	7.67 ± 1.33	3.85 ± 0.58	no_tx	No treatment during the study		
Mizuno et al., 2017. PLOS ONE. Japan, a university hospital	20	13/7	61.2 ± 9.2	NR	25.4 ± 3.6	7.5 ± 1.7	2.4 ± 0.5	SRP	OHI + SRP+ SPT at 3 and 6 m	3,6	In T2D patients, NSPT improved systemic oxidative stress balance and quality of lif, but did not decrease HbA1c levels at 3 months follow-up.
	17	15/2	62.8 ± 12.1	NR	27.0 ± 4.4	7.7 ± 1.2	2.4 ± 0.7	no_tx	OHI		
Tsobgny-Tsague et al., 2018. BMC Oral Health. Sub-Saharan Africa, a hospital	15	8/7	51.2 ± 7.8	60.0 ± 46.3 (mo)	29.2 ± 5.7	9.7 ± 1.6	3.0 ± 0.4	SRP	Immediate ultrasonic scaling, SRP with sub-G 10% povidone iodine irrigation	3	NSTP marakedly improved glycemic control with a attributable reduction of 2.2 point of HbA1c in poorly controlled T2D patients.
	15	5/10	51.7 ± 9.9	51.1 ± 39.6 (mo)	27.3 ± 5	8.9 ± 0.9	3.1 ± 0.6	no_tx	Delayed periodontal treatment for 3 mo		
Das et al., 2019. J Comtemp Dent Pract. India, Regional dental college and hospital	17	10/7	38 ± 11	NR	NR	7.58 ± 0.89	3.08 ± 0.30	SRP	SRP	3	the adjunct of doxycycline to conventional periodontal therapy provides additional benefit in reductin glycemic level and improves periodontal health.
	17	8/9	42 ± 13	NR	NR	8.42 ± 1.27	3.31 ± 0.62	SRP + Anti	SRP + doxycycline		
	17	11/6	40 ± 12	NR	NR	8.35 ± 0.96	3.42 ± 0.49	no_tx	No treatment		
El-Makaky et al., 2020. Oral Dis. Egypt, a university	44	18/26	52.95 ± 6.52	NR	NR	8.12 ± 0.74	4.99 ± 0.75	SRP + Anti	SRP, metronidazle 400 mg and amoxicillin 500 mg 3 times daily for 2 weeks, OHI	3	The NSPT using a combination of metromidazole and amoxicillin significantly improved the metabolic outcome in addition to periodontal health in T2D patients with periodontitis.
	44	20/24	52.23 ± 7.03	NR	NR	8.21 ± 0.71	5.01 ± 0.83	no_tx	Delayed periodontal treatment for 3 mo		

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Table 1 (*continued*)

Author, Year, Journal Country, Source	No.	gender (M/F)	Age (y/o)	Duration of T2D (yrs; mean ± SD)	BMI (kg/m^2; mean ± SD)	baseline HbA1C (%)	baseline PPD (mm)	group	Interventions	follow up (mo)	Conclusions
Qureshi et al., 2021. BMC Oral Health. Pakistan, a university hospital	50	30/20	52.72 ± 8.00	NR	26.66 ± 5.23	9.05 ± 1.70	3.64 ± 0.88	SRP + Anti	SRP + metronidazle 400 mg x 3 for 10 day + OHI	3	SRP improves glycemic control of T2D patients independently of the use of metronidazole.
	50	27/23	51.24 ± 8.27	NR	26.27 ± 3.61	9.05 ± 1.83	3.44 ± 0.95	SRP	SRP + OHI		
	50	25/25	52.82 ± 6.28	NR	25.72 ± 4.21	8.34 ± 1.26	3.04 ± 0.70	no_tx	OHI		

M, male; F, female; y/o, years old; T2D, type 2 diabetes; yrs, years; SD, standard deviation; BMI: body mass index; PPD, pocket probing depth; NR, not reported; mo, months; SRP, scaling and root planing; Anti: Antibiotics; no_tx.: no treatmen; OHI, oral hygiene instruction; LA, local anesthesia; hrs, hours; F/U, follow-ups; sub-G, subgingival; supra-G, supragingival; SPT, support periodontal therapy; NSPT, non-surgical periodontal treatment.

further reduction of PPD in response to SRPa, as compared to SRP, was also observed (SMD: −0.13 mm; 95% CI: −0.35/0.09; p = 0.241). The included studies did not show publication bias (Supplementary 4 & 5).

3.4.2. NMA

Although direct comparisons between any two study groups (SRP vs control, SRPa vs control and SRP vs SRPa) could be identified in included studies, NMA also provided indirect comparisons as an evidence of effects of SRP and SRPa. There was no inconsistency between direct and indirect comparisons. Compared to the control, interventions with SRP (SMD: −0.72%; 95% CI: −1.00/−0.43) or SRPa (SMD: −0.96%; 95% CI: −1.35/−0.58) achieved reductions in HbA1c. The effects of both SRP and SRPa were significant (both p < 0.001). SRPa did not reduce HbA1c more than SRP (SMD: −0.25%; 95% CI: −0.61/0.12; p = 0.1894). Reductions in PPD were also achieved by SRP (SMD: −0.67 mm; 95% CI: −0.84/−0.51) and SRPa (SMD: −0.89 mm; 95% CI: −1.12/−0.66) with significance (both p < 0.001) (Fig. 2). However, unlike the result of HbA1c, SRPa further reduced PPD compared to SRP (SMD: −0.22 mm; 95% CI: −0.43/−0.00) with significance (p = 0.0455).

3.5. Six-month changes in HbA1c and PPD

3.5.1. Pairwise meta-analysis

The pooled pre/post HbA1c and PPD change from 7 studies [7,18,25,27,28,33,36] with 9 comparison groups enrolling 943 participants was shown in Fig. 1. There was no comparison between SRPa and the control. Compared to the control, SRP reduced HbA1c (SMD: −0.29%; 95% CI: −0.56/−0.02) with significance (p = 0.033), while SRPa compared to SRP did not reduce with significance (SMD: −0.13%; 95% CI: −0.45/0.20; p = 0.439). Meanwhile, SRP reduced PPD, as compared to the control (SMD: −0.56 mm; 95% CI: −0.75/−0.37) with significance (p = 0.000). No further reduction in PPD by SRPa (SMD: −0.25 mm; 95% CI: −0.57/0.06; p = 0.111) was observed, when compared to SRP. The included studies did not show publication bias (Supplementary 4 & 5).

3.5.2. NMA

When there was no direct comparison between SRPa and control, NMA provided indirect evidence of the effects of SRPa, based on the result of the indirect comparison. The rest of comparisons (SRP vs. control and SRP vs. SRPa) showed no inconsistency between direct and indirect comparisons. Compared to the control, SRP reduced HbA1c (SMD: −0.29%; 95% CI: −0.55/−0.03) with significance (p = 0.0298). In contrast, SRPa did not significantly reduce HbA1c (SMD: −0.42%; 95% CI −1.00/0.17; p = 0.1657). Additionally, SRPa did not further reduce HbA1c when compared to SRP (SMD: −0.13%; 95% CI: −0.66/0.40; p = 0.6355). Meanwhile, both SRP (SMD: −0.56 mm; 95% CI: −0.74/−0.37) and SRPa (SMD: −0.81 mm; 95% CI: −1.22/−0.40) reduced PPD with significance (both p < 0.001) (Fig. 2). However, SRPa did not further reduce PPD when compared to SRP (SMD: −0.25 mm; 95% CI: −0.61/0.11; p = 0.1741).

3.6. Meta-regression

Whether heterogeneity in treatment effects was a result of initial DM control was further explored by meta-regression. The mean initial HbA1c was divided into two groups, fair control and poor control, defined by HbA1c < 9% and ≥ 9%, respectively. The mean initial HbA1c difference (fair control vs. poor control) was directly correlated with the HbA1c reduction difference (p < 0.001). The baseline HbA1c accounted for 65.32% of the effect heterogeneity, associated with a higher effect size. The periodontal intervention was directly correlated with the difference in PPD reduction (p = 0.0037). The

Table 2
Quality assessment of the included Systemic Review, according to Cochrane Collaboration RoB-2 tool.

		Rodrigues et al., 2003	Kiran et al., 2005	Singh et al., 2008	Al-Zahrani et al., 2009	Chen et al., 2012	Moeintaghavi et al., 2012	Miranda et al., 2014	Tsalikis et al., 2014	Wu et al., 2015	Kaur et al., 2015	Geisinger et al., 2016	Wang et al., 2017	Mizuno et al., 2017	Tsobgny-Tsague et al., 2018	Das et al., 2019	El-Makaky et al., 2020	Qureshi et al., 2021
Domain 1: risk of bias arising from the randomization process	1.1 was the allocation sequence random?	PY	PY	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	1.2 Was the allocation sequence concealed until participans were enrolled and assigned to interventions?	NI	NI	NI	NI	Y	NI	Y	Y	NI	NI	NI	NI	N	NI	Y	Y	Y
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Risk-of-bias judgement	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Domain 2: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	2.1. Were participants aware of their assigned intervention during the trial?	Y	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	PY	Y	Y	N	Y
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	Y	NI	Y	NI	Y	Y	N	N	Y	Y	Y	Y	N	Y	NI	Y	Y
	2.3. [If applicable:] If Y/PY/NI to 2.1 or 2.2: Were important non-protocol interventions balanced across intervention groups?	NI		NI		NI	NI			NI	NI	NI	NI	NI	NI		N	NI
	2.6. If N/PN/NI to 2.3, or Y/PY/NI to 2.4 or 2.5: Was an appropriate analysis used to estimate the effect of adhering to the intervention?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Risk-of-bias judgement	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	LOW RISK	LOW RISK	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN
Domain 3: Missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	PY	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Risk-of-bias judgement	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK

(*continued on next page*)

Table 2 (*continued*)

		Rodrigues et al., 2003	Kiran et al., 2005	Singh et al., 2008	Al-Zahrani et al., 2009	Chen et al., 2012	Moeintaghavi et al., 2012	Miranda et al., 2014	Tsalikis et al., 2014	Wu et al., 2015	Kaur et al., 2015	Geisinger et al., 2016	Wang et al., 2017	Mizuno et al., 2017	Tsobgny-Tsague et al., 2018	Das et al., 2019	El-Makaky et al., 2020	Qureshi et al., 2021
Domain 4: Risk of bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	NI	NI	NI	N	NI	N	N	N	NI	N	NI	N	N	N	N	N	N
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	PN	PN	PN		PN				PN		PN						
	Risk-of-bias judgement	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Domain 5: Risk of bias in selection of the reported result	5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	5.2. multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	5.3. multiple eligible analyses of the data?	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Risk-of-bias judgement	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK	LOW RISK
Overall risk of bias	Risk-of-bias judgement	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	LOW RISK	LOW RISK	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN	SOME CONCERN

PY: Probably Yes; NI: No Information; N, No; Y: Yes; PN: Probably No.
Scientific field of dental science: Periodontology

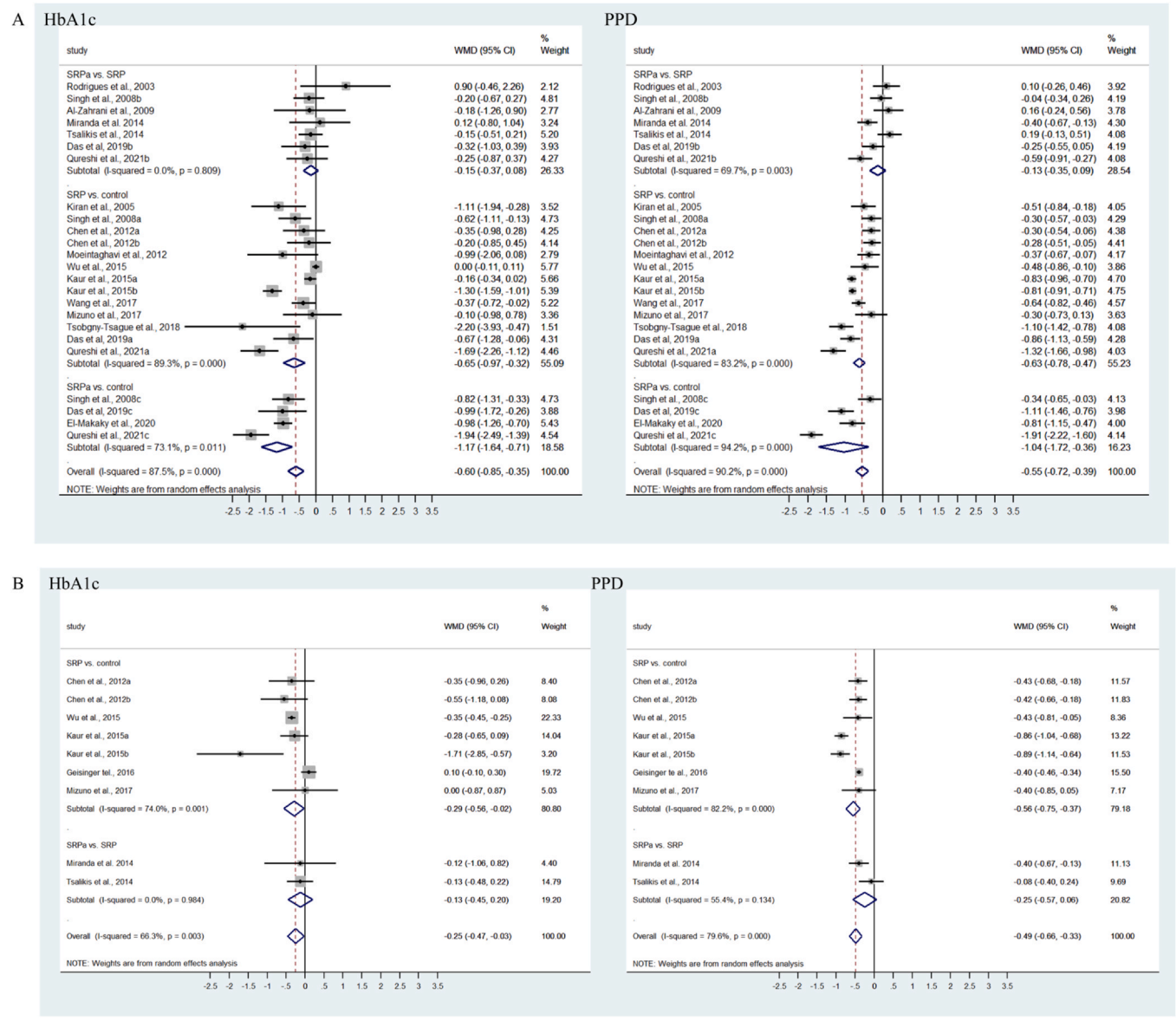

Fig. 1. Forest plots of the pairwise meta-analysis of reductions in (A) HbA1c and PPD at 3-month postintervention, (B) HbA1c and PPD at 6-month postintervention compared to the control.

periodontal intervention accounted for 46.76% of the effect heterogeneity and was associated with a larger effect size.

3.7. Sensitivity analyses

To test the robustness of the result based on systemic review involving a process of decision making, sensitivity analyses were performed by omitting one data set in each step or omitting specific data sets. (Supplementary 6).

3.7.1. 3-month postintervention

Removing any of the included studies did not change the main results.

3.7.2. 6-month postintervention

Removing studies of Chen et al. [22], Kaur et al. [25], or Wu et al. [36] led to the no significant reduction in HbA1c by SRP, in respect to the control. On the other hand, if the study by Tsalikis et al. [33] was excluded, SRPa became able to further reduce PPD, as compared to SRP.

4. Discussion

4.1. Review findings

In the acute inflammatory phase, patients often receive systemic antibiotics to control inflammation. However, for chronic inflammatory diseases such as T2D and periodontitis, it is unclear whether the addition of systemic antibiotics to periodontal treatment will have better results. As systemic inflammation is a significant burden for T2D patients, clarifying the association between periodontitis and systemic inflammation could thus help manage T2D patient with periodontitis. To our knowledge, this is the first study to quantitatively summarize patients with T2D and periodontitis to assess whether systemic antibiotics as adjuvants to SRP are effective in both diseases, in terms of HbA1c and PPD.

Several association pathways between periodontitis and systemic inflammation had been proposed. First, increasing neutrophil and pro-inflammatory mediators, such as IL-1, IL-6, C-reactive protein (CRP) and fibrinogen, in the bloodstream of periodontal patients could result in low-grade systemic inflammation [1]. Second,

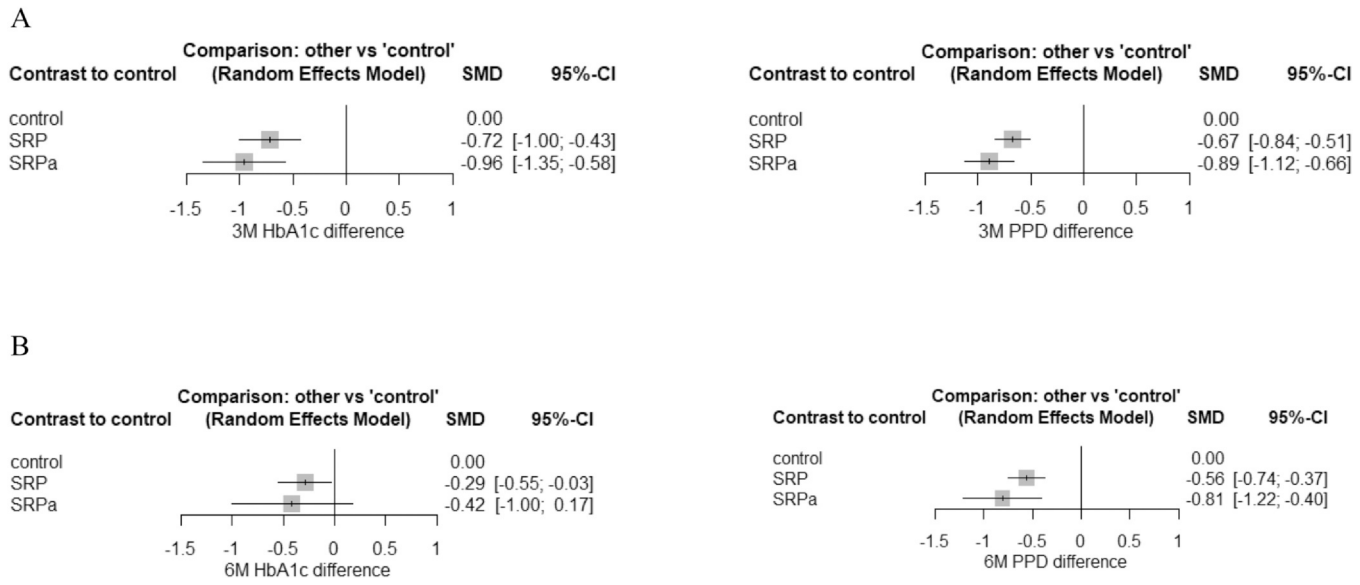

Fig. 2. Forest plots of the network meta-analysis of reductions in (A) HbA1c and PPD at 3 months postintervention, (B) HbA1c and PPD at 6 months postintervention compared to the control.

periodontal bacteria or their mediators enter periodontal tissue through the ulcerated epithelium of periodontal pockets and then disseminate into the bloodstream could lead to bacteremia [37]. Third, the causative bacteria of periodontitis that reach the gastrointestinal tract through oro-digestive translocation could cause intestinal dysbiosis and gut-mediated systemic inflammation [38]. Therefore, the addition of systemic antibiotics to periodontal treatment was targeting periodontal pathogens to reduce both local and systemic inflammation. As a previous meta-analysis showed that changes in clinical periodontal parameters were independent of the types of antibiotic adjuncts [39], the effects of systemic antibiotics used in the included studies were considered the same in this NMA.

The main findings of this systematic review and meta-analysis showed that SRP and SRPa were effective in reducing PPD and HbA1c 3 months after treatment in patients with T2D and periodontitis. At 6-month follow-up, SRP still reduced PPD and HbA1c, but SRPa only reduced PPD. SRP is considered the gold standard treatment for periodontitis. SRP controls periodontal inflammation via mechanically destroying the biofilm structure and disrupting the local ecological niche of bacteria in both supraginival and subgingival areas. Previous studies had shown that clinical periodontal changes were relatively accompanied by specific changes in the subgingival microbiota [40]. For instance, periodontal pathogens, such as *Bacteroides forsythus* and *Porphyromonas gingivalis*, and suspected pathogens *Treponema denticola* and *Streptococcus constellatus*, were significantly reduced in prevalence, proportions, and levels after SRP. Compared to pretreatment levels, the most profound reduction in PPD and microbial changes occurred during the first 3 months after SRP, although *Bacteroides forsythus*, *Porphyromonas gingivalis*, and *Treponema denticola* continued to significantly decrease prevalence and levels at 12 months [41]. Our results also showed that the reduction in PPD was greater at 3-month after SRP than at 6-month after SRP.

In addition to reducing PPD, SRP was shown to reduce the plasma level of CRP and HbA1c in patients with T2D and periodontitis [42]. This study further revealed that SRP alone was able to reduce HbA1c even by 0.72% at 3 months after intervention, which is in fact comparable to the effect of 1000 mg metformin XR once daily for 3 months [43]. Consequently, SRP could thus be used as an important adjuvant, such as diet control, exercise, oral medications, and insulin injections, for T2D therapy. To clarify the contribution of SRP in glycemic control, further prospective studies could be designed to compare the effect of SRP and the second medication for individuals. However, at 6 months after SRP (−0.29%, 95% CI −0.55 to −0.03, $p < 0.001$), the amount of HbA1c reduction was significantly less (−0.72%, 95% CI −1.00 to −0.43, $p < 0.001$) than that at 3 months after SRP. The finding could have two possible explanations. First, there was a decrease in the efficacy of systemic inflammation reduction of SRP with time. Second, in this study, the association with the amount of HbA1c reduction may depend on the initial HbA1c level. Since seven [18,25,27,29–31,34] of the 15 studies [18,22,23,25–36] had an initial HbA1c of 8 ~ 9% at 3 months after SRP. In contrast, at 6 months after SRP, only two [22,25] of the five studies [7,22,25,28,36] had an initial HbA1c of 8 ~ 9% and that in the remaining studies was less than 8%. Thus, the magnitude of reductions in HbA1c at 6 months was smaller than that at 3 months. This inference was partially supported by previous findings that the higher the baseline HbA1c, the more HbA1c decreased after non-surgical periodontal therapy [44]. For this reason, patients with poor glycemic control are highly recommended to receive SRP every 3 months, which may result in a substantial improvement in glycemic control.

As adjuvants to SRP, systemic antibiotics rely on a broad or selective bactericidal ability to reduce the number of bacteria in periodontal pockets or alter the bacterial phase of dental plaque. For example, the SRP group with metronidazole and amoxicillin (MTZ +AMX) exhibited greater reductions in all species of the red complex and two putative pathogens (*Ebacterium nodatum* and *Prevotella intermedia*) of the orange complex at 3 months postoperatively compared to the SRP group alone. Furthermore, the microbiological benefits of MTZ plus AMX are not limited to periodontal deep pocket, but also extend to shallow pockets which may also harbor high levels and proportions of periodontal pathogens [27]. As most microbiological benefits could last up to 1 year [27], however, SRPa demonstrated a significant reduction in PPD at 3-month post-intervention ($p = 0.0455$), but not at 6-month post-intervention, as compared to SRP alone in this study. Regarding the result of the sensitivity test, in which omitting the study of Tsalikis et al. [33] led to more reduction in PPD by SRPa than by SRP, it is suggested that including these papers were somewhat arbitrary or unclear. Nevertheless, following the screen strategy, only two papers that

published the effects of SRPa were eligible to enter this study. This indicated that further research should be conducted to explore the long-term effects of SRPa on PPD.

The microbiological benefits of systemic antibiotics could also influence blood sugar control in DM patients, as adjuvants to SRP, systemic antibiotics might affect gut microbiome related inflammatory and insulin signaling, thereby improving insulin sensitivity and glucose homeostasis [45]. For example, doxycycline has been shown to reduce CRP and myeloperoxidase in the plasma of patients with T2D [46]. Ampicillin and metronidazole induced microbiome depletion, which was characterized by a reduction in luminal *Firmicutes* and *Bacteroidetes* species, decreases of fasting glucose levels, and glucose surging during glucose tolerance tests [47]. In the present study, the treatment effect of SRPa was great 3 months postoperatively, which revealed a substantial reduction of 0.96% in T2D patients with an initial HbA1c of 8–9%. However, compared to the 0.72% reduction at 3-month postintervention by SRP alone, the synergetic effect did not reach the significance level. Similar findings were also reported in a meta-analysis by Cao et al. [48] and Wang et al. [15]. Although SRP with systemic antibiotics was not statistically greater than SRP alone in HbA1c reduction in this study, optimizing the synergistic effect of SRP and systemic antibiotics has potential for further research.

Interestingly, SRP alone could still reduce PPD and HbA1c at 6-month follow-up; however, SRPa only reduced PPD but not HbA1c. A possible reason for the lack of HbA1c reduction at 6-month follow-up is that the effect of adjuvant antibiotics on the gut microbiota was temporary, as the gut microbiota could recover within 4 weeks after antibiotic treatment [49]. It was hypothesized that the adverse effect of the recovered gut microbiota might diminish the overall treatment outcomes [50]. Another reason could be that only two studies have been published at 6-month follow-up after SRPa treatment [27,33]. Both studies concluded that there were no statistically significant changes in HbA1c after treatments, either with SRP alone or with SRPa. Miranda et al. [27] attributed this to the fact that the calculation of the experiment sample size was not based on changes in glycemic parameters and suggested that a larger sample size may be required to achieve significant changes in HbA1c levels after periodontal treatment. On the other hand, another study by Tsalikis et al. included only individuals with well-controlled diabetes, so it is reasonable that HbA1c would not improve significantly after treatment [33]. To further explore the effect of SRPa treatments on HbA1c reduction at 6-month follow-up, we look forward to more RCTs with longer follow-ups after SRP or SRPa treatments.

4.2. Limitations

This NMA has some limitations. First, due to ethical considerations, there was no way to leave patients untreated for too long. Thus, the included studies regarding the effect of SRPa had a rather short-term follow-up. Most of the studies had a follow-up duration of 3 months and few of them within 6 months. Second, important confounding factors affecting glycemic control, such as smoking, BMI, and diet, should be adjusted in included studies, but these data were not always available. Another critical issue was that different inclusion criteria (Supplementary 3) may have influences on the findings; however, the severities of T2D and periodontal disease were not well graded in this NMA. Future studies should include individuals with a wide range of periodontal severity to evaluate whether control of gingivitis or mild/moderate/severe periodontitis has an impact on T2D patients with different levels of HbA1c.

4.3. Implications for practice

It is obvious that controlling systemic inflammation is beneficial for T2D patients. However, the current clinical trials of using small molecule anti-inflammatory approaches or biological agents for target specific pro-inflammatory cytokine pathways were still controversial. In view of the outputs of this systematic review and meta-analysis, SRP or SRPa demonstrated promising results in control periodontitis and HbA1c of T2D patients, which might be attributed to the decrease of systemic inflammation. Therefore, regular SRP or SRPa should be advised for the patients with poor glycemic control.

5. Conclusions

SRP and SRPa were effective in reducing PPD and HbA1c in patients with T2D and periodontitis at 3 months after treatment. The adjunctive effect of antibiotics was obvious in reducing both PPD and HbA1c, but only PPD reaches the significance level. At 6 months, SRP alone still showed significant reductions in PPD and HbA1c, however, it was less efficient compared to the results at 3 months after SRP. While SRPa revealed controversial results, which needs more studies to clarify. Based on the findings of this NMA, we strongly recommend that patients with diabetes should consider receiving periodontal therapy and periodontal maintenance at least every 3 months to control periodontal and glycemic status. For patients with poor glycemic control, physicians are encouraged to refer the patients to dentists for periodontal assessment and treatment, and dentists should work with physicians to provide comprehensive care for T2D patients.

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Conflicts of interest

The authors declare no conflict of interest.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jdsr.2023.06.001.

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