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Effects of Periodontal Treatment on Glycemic Control in Type 2 Diabetic Patients: A Meta-Analysis of Randomized Controlled Trials

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Abstract

The association between diabetes and inflammatory periodontal diseases has been studied extensively. However, there is a lack of robustness and homogeneity among studies describing effects of periodontal treatment on glycemic control. The aim of this study was to carry out a meta-analysis to understand whether periodontal treatment could improve glycemic control in type 2 diabetic patients. Electronic searches were carried out on MEDLINE, EMBASE and the Cochrane central register of controlled trials from 1980 to July 2012. Randomized controlled trials of periodontal therapy on glycemic control in diabetic patients with a minimum of 3 months of follow-up were included. Meta-analysis was carried out with 8 studies involving 515 participants using Stata 11.0 software. Our results showed that periodontal treatment could lead to a significant decrease in HbA1c level. The standardized mean difference between intervention groups and control groups was significant: 1.03% (95% confidence interval: 0.31% to 1.70%, $P = 0.003$) from baseline to 3 months, and 1.18% (95% confidence interval: 0.72% to 1.64%, $P < 0.001$) from baseline to 6 months. Periodontal treatment could lead to a non-significant decrease in fasting plasma glucose (FPG) levels from baseline to 3 months. The standardized mean difference between the intervention and the control group was 0.69 mg/dl (95% confidence interval: -0.27 mg/dl to 1.66 mg/dl, $P = 0.158$). Our analysis indicated that periodontal treatment could improve glycemic control in type 2 diabetic patients with periodontal diseases.

Key Words: diabetes, glycosylated hemoglobin, meta-analysis, periodontal treatment

Introduction

Diabetes mellitus (DM) and periodontal disease are highly prevalent chronic diseases that have a major impact on the health and well being of millions of individuals worldwide (2, 13). A large number of case

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reports, cross-sectional studies and longitudinal studies previously reported the adverse effects of diabetes on the onset, progression and severity of periodontitis (7, 27, 49, 51). Several lines of evidence support the fact that periodontal infection affects glycemic control and increases the risk of diabetic complications (36, 40). Recent studies also suggest that diabetic patients with severe periodontal disease are six times more likely to have poor glycemic control (52, 53).

Treatment of periodontitis includes mechanical removal of supra- and sub-gingival bacterial plaque with scalers, curettes or ultrasonic devices (scaling and root planing [SRP]). Antibiotics are used as an adjunctive therapy to SRP to prevent re-infection. The potential effects of periodontal therapy on glycemic control of diabetic patients have been investigated by numerous interventional trials (6, 10, 29, 57). Several studies showed that non-surgical periodontal treatment could reduce the level of glycosylated hemoglobin (HbA1c) in these patients (9, 34, 41). Some studies reported SRP in conjunction with antibiotics resulted in periodontal clinical benefits without a significant reduction in the glycemic control of diabetic subjects (8, 20, 44). The latest systematic review and meta-analysis suggested that periodontal treatment leads to an improvement of glycemic control in DM patients for at least 3 months (54). Although several studies reported that surgical and non-surgical periodontal treatment decreased systemic inflammatory burden allowing better glycemic control, other studies did not report significant improvements (16). There is also a lack of robustness and homogeneity among different studies. The effects of periodontal therapy on diabetes control in geriatric patients and its long term benefits are still not known.

In the present meta-analysis, we attempted to increase the power of the study to identify the effects of periodontal treatment on glycemic control sustained for 6 months in a randomized controlled study group of type 2 diabetic patients with periodontal disease.

Materials and Methods

Data Sources and Searches

Three databases, MEDLINE (*via* PubMed), EMBASE and the Cochrane Database of Systematic Reviews were searched using key words and Medical Subject Headings terms, and the Boolean operators "OR" and "AND": ["periodontal disease" OR periodontitis OR "periodontal infection" OR periodont] AND ["diabetes" OR diabetic OR NIDDM OR IDDM OR T1DM OR T2DM] AND [therapy OR treatment OR intervention]; the databases searched were dated from January 1980 to 31 July 2012. We combined these terms and limited the search to humans and the English language. In addition, manual searches of the references from selected original research and review articles were also conducted.

Study Selection

To be included in this meta-analysis, the studies had to meet the following criteria: [1] original investigations, excluding review articles and meta-analyses; [2] intervention studies containing diabetic patients with periodontitis, receiving periodontal treatment with or without adjunctive antimicrobial therapy, and control groups receiving no periodontal treatment, controlled clinical trials or randomized clinical trial designs, and outcome measures of glycemic controls; [3] a duration of study of at least 3 months.

Potentially relevant publications were independently reviewed by two investigators (QYS and MZZ) and decisions were made by them on inclusion. Additional investigators were involved to discuss any arising discrepancies until a mutual agreement was reached.

Data Extraction and Quality Assessment

Data extraction and quality assessment of selected studies were performed independently and in duplicates by two trained and blinded investigators. A standard piloted data extraction template was used to collect the following data: primary author's name, year and source of publication, country of origin, study design, method of sampling and grouping, characteristics of the study population, inclusion criteria of diabetes, inclusion criteria of periodontal disease, method of intervention, study duration, mean and standard deviation of outcomemeasures. The authors were contacted for additional or missing data if necessary.

The quality of the methodologyl of the studies was assessed according to the Cochrane Handbook for Systematic Reviews of Interventions (Cochrane Library, http://www.cochrane-handbook.org, Chapter 8). The following parameters were considered: blinding of participants and personnel, concealment of treatment allocation, quality of randomization, reporting of withdrawals and loss to follow up.

Data Synthesis and Analysis

Statistical analyses were conducted according to the Cochrane Collaboration and Quality of Reporting of Meta-Analyses (QUOROM) guidelines (33). The meta-analysis was performed using Stata software, version 11.0. The primary outcome was the change in HbA1c between baseline and endpoint in response to periodontal intervention. For trials that did not state the absolute differences of HbA1c

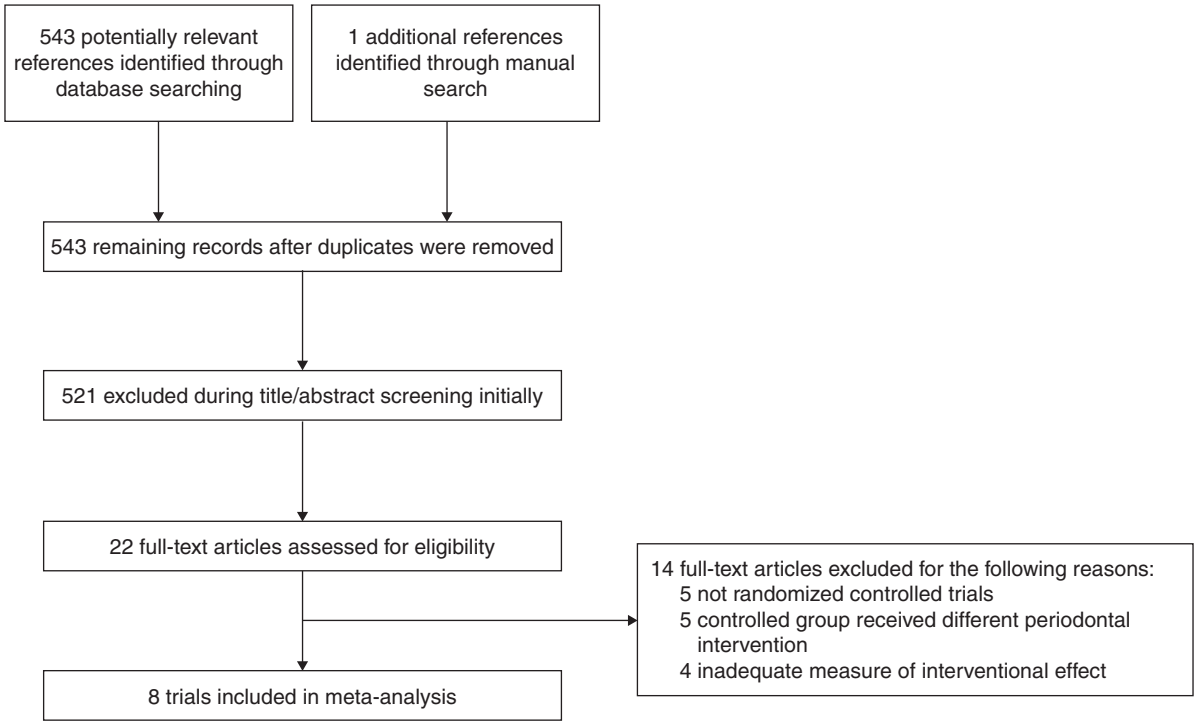

Fig. 1. Flow chart of study selection.

(Δ%HbA1c) between baseline and endpoint in two groups, the differences were calculated according to Fundamentals of Biostatistics (5th Edition): Δ%HbA1c = $\%A1c_{ti1} - \%A1c_{ti2}$. The standard deviation (SD) of Δ%HbA1c$_{ti}$ (S_{ti}) was estimated as follows: $S_{ti}^2 = S_{ti1}^2 + S_{ti2}^2 - 2r \bullet S_{ti1} \bullet S_{ti2}$ (18), where %HbA1c$_{ti1}$ is the mean %HbA1c value of baseline level and $\%A1c_{ti2}$ is the mean %HbA1c value after treatment, S_{ti}^2 is the variance of Δ%HbA1c, S_{ti1}^2 is the variance of the mean baseline %HbA1c values, S_{ti2}^2 is the variance of the mean end %HbA1c values, r is the correlation between the baseline and end values, S_{ti1} and S_{ti2} are the SDs of the baseline and end values respectively; the closer |r| is to 1, the more closely related the variables are; if |r| = 1, then one variable can be predicted exactly from the other. We assumed r to be 0.5 as was previously described (18).

Statistical heterogeneity across trials was assessed with the χ^2-test ($P < 0.1$) and the I^2 statistic (14). The I^2 statistic measures the proportion of overall variation that is attributable to between-study heterogeneity. The heterogeneity test was considered statistically significant if the P-value was under 0.1. Heterogeneity was considered high if the I^2-value was above 50%. Tau^2 was calculated in order to determine the size and clinical relevance of heterogeneity when detected by the previous calculations (42). A random-effects model was used to calculate the effect sizes if I^2-value was above 50%. The possible reasons of heterogeneity were determined by examining the characteristics of each study.

Results

The flow chart of the study selection is shown in Fig. 1. The initial research retrieved 544 potentially relevant articles. One repeated article was excluded. From the remaining 543 articles, 521 were excluded because they were either review articles or were not clinical trials or to the present meta-analysis, or were animal studies or cellular studies. A total of 22 full-text articles were evaluated for inclusion. Eight randomized controlled studies met all of the eligibility criteria and were included in this meta-analysis (15, 23-25, 32, 38, 47, 48).

General Characteristics

The eight studies included data from 515 trial participants (265 in the intervention group and 250 in the control group). The baseline characteristics of these studies are summarized in Table 1. Two of these studies were published in a medical journal (15, 48), and six were published in periodontal, dental or oral health journals (23-25, 32, 38, 47). All trials were conducted between 2001 and 2012. One study was from North America (47), five were conducted in Asia (two in China, one each in Iran, Jordan and Thailand) (15,

Table 1. Characteristics of studies included in the meta-analysis and change in HbA1c and FPG values.

First Author, Publication, Year	Country	Mean Age (Year)	Inclusion Criteria of Diabetes, Initial HbA1c (%), Diabetes Duration (Year)	Inclusion Criteria of Periodontal Disease	Sample Size	Interventions	Intervention Duration (Month)	Outcome Measures	Results:changes in HbA1c (%)/ FPG (mg/dl)
Stewart, J.E. J. Clin. Periodontol., 2001	United States	I: 62.40 ± 8.40 C: 67.30 ± 10.80	Inclusion Criteria: T2DM with HbA1c 10.0%~15.9%, Initial HbA1c: I: 9.20 ± 2.20 C: 8.50 ± 2.10 Diabetes Duration: I: 9.50 ± 2.20 C: 8.50 ± 2.10	No reporting	I: 36 C: 36	I: SRP + OHI + removal of teeth C: No treatment	9	HbA1c	HbA1c Changes: I: 1.90 ± 0.30 C: 0.80 ± 0.60 $P = 0.02$
Kiran, M. J. Clin. Periodontol., 2005	Turkey	I: 55.95 ± 11.21 C: 52.82 ± 12.27	Inclusion Criteria: *1*) T2DM with HbA1c 6.0%~8.0%. *2*) Creatinine < 1.4 mg/dl. *3*) Liver function tests not up to 3 times normal range. *4*) No major diabetic complications. Initial HbA1c: I: 7.31 ± 0.74 C: 7.00 ± 0.72 Diabetes Duration: I: 9.32 ± 8.36 C: 8.05 ± 5.90	*1*) No history of systemic antibiotic administration within the last 3 months. *2*) No periodontal treatment 6 months prior to the study.	I: 22 C: 22	I: SRP + OHI C: No treatment	3	HbA1c FPG 2hPPG	HbA1c Changes: I: 0.80 ± 0.77 C: -0.31 ± 1.83 $P = 0.03$ FPG Changes: I: 3.96 ± 30.58 C: -1.22 ± 37.49 $P = 0.48$ 2hPPG Changes: I: 23.59 ± 48.46 C: -2.18 ± 67.85 $P = 0.07$
Promsudthi, A. Oral Dis., 2005	Thailand	I: 61.11 ± 5.83 C: 61.64 ± 5.81	Inclusion Criteria: T2DM with HbA1c 7.5%~11.0%, Initial HbA1c: I: 8.98 ± 0.88 C: 9.17 ± 1.02 Diabetes Duration: I: 8.30 ± 4.21 C: 14.36 ± 7.57	Total teeth ≥ 14 with ≥ 8 sites with PPD ≥ 5 mm and CAL ≥ 5 mm	I: 27 C: 25	I: SRP + OHI + Doxy 100 mg daily C: No treatment	3	HbA1c FPG	HbA1c Changes: I: 0.19 ± 0.74 C: -0.12 ± 1.05 $P > 0.05$ FPG Changes: I: 3.63 ± 35.55 C: -0.2 ± 54.22 $P > 0.05$
Khader, Y.S. J. Periodont. Res., 2010	Jordan	I: 57.1 ± 6.90 C: 55.6 ± 7.90	Inclusion Criteria: T2DM with HbA1c ≥ 7.0%, Initial HbA1c: I: 8.64 ± 1.24 C: 7.73 ± 0.87 Diabetes Duration: I: 7.70 ± 4.20 C: 8.10 ± 4.50	Total teeth ≥ 8 in a hopeless condition	I: 26 C: 24	I: Full-mouth tooth extraction + dentures C: No treatment	3, 6	HbA1c FPG	HbA1c Changes (3 Mons): I: 1.23 ± 0.79 C: 0.28 ± 0.87 $P = 0.00$ HbA1c Changes (6 Mons): I: 1.37 ± 1.00 C: 0.28 ± 0.70 $P < 0.00$ FPG Changes: a similar pattern of change to that for HbA1c.

Table 1. (Continued)

First Author, Publication, Year	Country	Mean Age (Year)	Inclusion Criteria of Diabetes, Initial HbA1c (%), Diabetes Duration (Year)	Inclusion Criteria of Periodontal Disease	Sample Size	Interventions	Intervention Duration (Month)	Outcome Measures	Results:changes in $HbA1_c$ (%)/ FPG (mg/dl)
Koromantzos, P.A. J. Clin. Periodontol., 2011	Greece	I: 59.62 ± 7.95 C: 59.42 ± 9.80	Inclusion Criteria: T2DM with HbA1c 7.0% ~10.0%, Initial HbA1c: I: 7.00~9.90 C: 7.00~10.20 Diabetes Duration: I: 7.76 ± 4.33 C: 7.84 ± 6.80	Total teeth ≥16 with 8 sites with PPD ≥ 6 mm and 4 sites with CAL ≥ 5 mm, distributed in ≥ 2 different quadrants	I: 30 C: 30	I: SRP + OHI + teeth extraction C: OHI + S	3, 6	HbA1c	HbA1c Changes (3 Mons): I: 0.73 ± 0.66 C: 0.18 ± 0.59 $P < 0.05$ HbA1c Changes (6 Mons): I: 0.72 ± 0.93 C: 0.13 ± 0.46 $P < 0.01$
Sun, W.L. Intern. Med., 2011	China	I: 55.13 ± 11.16 C: 54.23 ± 10.85	Inclusion Criteria: *1*) T2DM with HbA1c 7.5%~9.5%. *2*) Diabetes duration ≥ 1 year. *3*) BMI (kg/m^2): 19~26 in women, 20~27 in men. *4*) No medication changes during study. *5*) No smoking. *6*) Without severe complications.	*1*) Total teeth ≥ 20, PPD > 5 mm, >30% teeth with AL > 4 mm, or >60% teeth with PPD > 4 mm and AL > 3 mm. *2*) Without periodontal treatment in the last 6 months. *3*) Without antibiotics or non-steroidal anti-inflammatory drugs administered in the last 3 months.	I: 82 C: 75	I: SRP + OHI + periodontal flap surgery + teeth extraction + Tinidazole 1.0 g, bid and ampicillin 0.25 g, qid C: No treatment	3	HbA1c FPG	HbA1c Changes (3 Mons): I: 0.50 ± 0.18 C: 0.14 ± 0.12 $P < 0.01$ FPG Changes: I: 21.06 ± 8.82 C: 7.92 ± 4.32 $P < 0.01$
Moeintaghavi, A. Aust. Dent. J., 2012	Iran	Average Age 50.29 ± 3.00	Inclusion Criteria: *1*) T2DM with HbA1c > 7.0%. *2*) No major diabetic complications. *3*) Blood Sugar control with glyben glamide and metformin, without insulin administration.	*1*) Mild to moderate periodontitis. *2*) No systemic antibiotic administration or periodontal treatment within the last 6 months.	I: 22 C: 18	I: SRP + OHI + placement of emergency restorations + teeth extraction + periodontal curettes C: OHI + placement of emergency restorations + teeth extraction	3	HbA1c FPG	HbA1c Changes: I: 0.74 ± 1.18 C: -0.25 ± 2.05 $P = 0.00$ FPG Changes: I: 17.5 ± 48.91 C: -9.78 ± 38.02 $P = 0.00$
Hong, Y. Chin. J. Geriatr., 2005	China	I: 64.00 ± 3.00 C: 64.00 ± 3.00	Inclusion Criteria: *1*) T2DM with HbA1c > 8.0%. *2*) Diabetes duration > 1 year. *3*) No serious diabetic complications.	*1*) Total teeth ≥ 15 with 6 sites with PPD ≥ 6 mm. *2*) Full mouth dental radiograthy: many sites with alveolar resorption surpass 1/2 tooth root. *3*) No periodontal treatment within the last 6 months.	I: 20 C: 20	I: SRP + OHI + S + 0.12% CHX rinses twice daily C: OHI	6	HbA1c	HbA1c Changes: I: 1.26 ± 0.80 C: 0.08 ± 0.65 $P < 0.01$

Values are presented as means ± SD. $P < 0.05$, $P < 0.01$ significant different to the control group. I: intervention group, C: control group, BMI: body mass index, OHI: oral hygiene instructions, S: supragingival removal of all deposits, CHX: chlorhexidine, Doxy: doxycycline. "+" indicates "and".

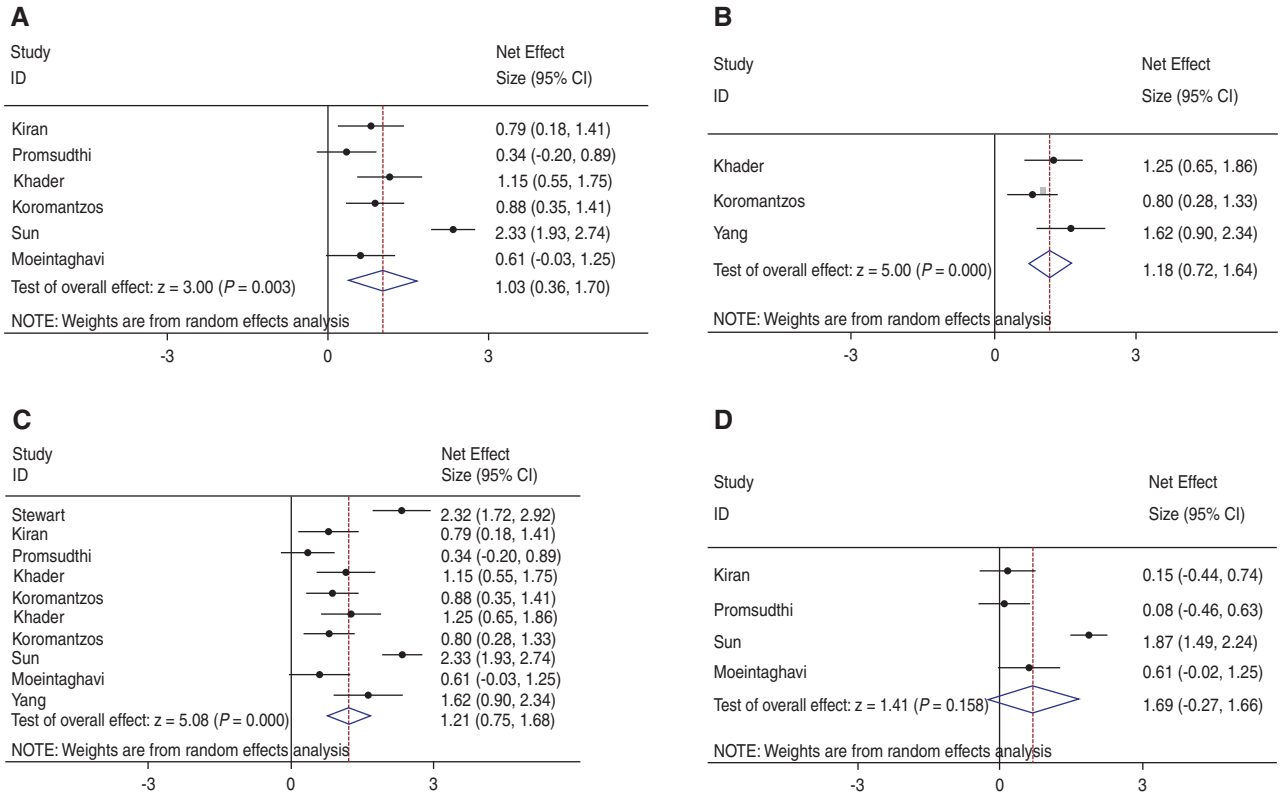

Fig. 2. Meta-analysis of periodontal treatment on HbA1c and FPG. A. Standardized mean differences (95% CI) of HbA1c between baseline and 3 months (%). B. Standardized mean differences (95% CI) of HbA1c between baseline and 6 months (%). C. Standardized mean differences (95% CI) of HbA1c duration study (%). D. Standardized mean differences (95% CI) of FPG between baseline and 3 months (%). $P < 0.01$ indicates a significant difference as compared with the control group.

23, 32, 38, 48), and one each in the Middle East (Turkey) (24) and Europe (Greece) (25). The sample size ranged from 18 to 82. The mean age of the trial groups ranged from 50.29 ± 3.00 to 67.30 ± 10.80 years. All studies provided entry criteria for DM, HbA1c values and the duration of diabetes. The mean baseline HbA1c level ranged from 7.00 ± 0.72% to 9.20 ± 2.20%. Most of studies provided inclusion criteria for periodontal disease (15, 23-25, 32, 38, 48). In some studies, periodontal treatment was not given within the last 6 months (23-25, 48). All studies provided non-surgical periodontal therapy as the intervention with (15, 38, 48) or without (23-25, 32, 47) local or systemic administration of antibiotics. The duration of intervention ranged from 3 to 9 months.

Bias Risk Assessment

There were different levels of bias in the 8 randomized controlled trials included in the analysis. Six studies conducted adequately randomized grouping (23-25, 32, 38, 48), and other studies conducted inadequately randomized grouping (15) or without describing specific grouping method (47). Two studies performed allocation-concealment (25, 32). Five studies were blinded for the evaluator (24, 25, 32, 38, 47), and other studies were not definite about the evaluator blinding criteria (15, 23, 48). Two studies reporting 8 and 33 participants were lost to follow-up or were withdrawn from the study (23, 48).

Meta-Analysis

The effects of periodontal treatment on glycemic control could be analyzed from the available intervention studies. Six studies could provide changes in the HbA1c level from baseline to 3 months (23-25, 32, 38, 48), three studies from baseline to 6 months (15, 23, 38), and one study from baseline to 9 months (47). Four studies could provide changes in the FPG level from baseline to 3 months (24, 32, 38, 48).

The meta-analysis revealed that periodontal treatment significantly decreased the level of HbA1c. The random effect model gave a standardized mean HbA1c differences from baseline to 3 months between the intervention and control group: 1.03% (95% CI: 0.36%, 1.70%), test of overall effect: z = 3.00 (P = 0.003). Heterogeneity was found among the six studies: I^2 = 89.0%; Tau^2 = 0.63; $P < 0.001$ (Fig. 2A). This fixed effect model estimated a standardized mean HbA1c

differences from baseline to 6 months between the intervention and the control group, as demonstrated, 1.18% (95% CI: 0.72%, 1.64%), test of overall effect: z = 5.00 ($P < 0.001$). The results of the χ^2 test showed no significant heterogeneity among the three studies: $I^2 = 41.2\%$; $Tau^2 = 0.07$; $P = 0.183$ (Fig. 2B). With random effects meta-analysis across all of the eight studies with a study duration of 9 months, there was a standardized mean difference in the level of HbA1c between the intervention and the control group: 1.21% (95% CI: 0.75%, 1.68%), test of overall effect: z = 5.08 ($P < 0.001$). The heterogeneity was found among the eight studies: $I^2 = 85.4\%$; $Tau^2 = 0.48$; $P < 0.001$ (Fig. 2C).

The result of meta-analysis showed a non-significant decrease in the level of FPG. The random effect model gave a standardized mean FPG differences from baseline to 3 months between the intervention and the control group: 0.69 mg/dl (95% CI: -0.27 mg/dl, 1.66 mg/dl), test of overall effect: z = 1.41 ($P = 0.158$). The heterogeneity was found among the four studies: $I^2 = 92.6\%$; $Tau^2 = 0.89$; $P < 0.001$ (Fig. 2D).

Discussion

Diabetes has many adverse effects on the periodontium, and conversely periodontitis may have deleterious effects further aggravating the condition in diabetics. The potential common pathophysiologic pathways include those associated with inflammation, altered host responses, altered tissue homeostasis and insulin resistance. Type 2 diabetes (T2DM) is a result of resistance to insulin combined with a failure to produce enough insulin to compensate for the resistance resulting in hyperglycemia (30, 44). Periodontal disease is a chronic inflammatory disease caused by oral infection with anaerobic gram-negative bacteria resulting in gingival inflammation, loss of attachment, bone destruction, and eventually the loss of teeth in severe cases. Bacteria produce endotoxins in the form of lipopolysaccharides (LPS) that are instrumental in generating a host-mediated tissue destructive immune response (28, 35). The association between periodontal diseases and diabetes has been explored by many researchers over the years. Extensive studies have shown that incidences of diabetes and periodontal disease share common risk factors and enhance the risk of each other (8, 39).

There are multiple underlying mechanisms by which T2DM is associated with periodontal diseases. The cells involved in immune response, including neutrophils, monocytes and macrophages, are altered in diabetic patients (4). Since the innate immune cells are the first line of host defense, inhibition of their functions may prevent the elimination of bacteria in the periodontal pocket, thereby increasing periodontal destruction. Elevated production of proinflammatory cytokines such as tumor necrosis factor α (TNF-α) is seen in diabetic patients in response to periodontal pathogens, which may increase host tissue destruction. Altered wound healing is one of the most common complications of diabetes (43). In a glucose-rich environment, the reparative capacity of periodontal tissues is also compromised. It has been suggested that hyperglycemia, a major consequence of T2DM, exacerbates the inflammatory process of periodontal diseases by promoting the accumulation of the receptor for advanced glycated end-products (RAGE) and the toll-like receptor4 (TLR4) ligands within the periodontium (12, 22). In diabetic patients, proteins become glycated to form advanced glycation end products (AGE). Interactions between AGEs and their receptors on inflammatory cells result in the increased production of proinflammatory cytokines such as interleukin-1β (IL-1β) and TNF-α (45). This interaction causes marked elevation of IL-1β and TNF-α in gingival crevicular fluid in diabetic patients with periodontitis (43). Several studies have indicated that circulating monocytes from diabetic patients exhibit an exaggerated inflammatory response to gram-negative bacterial LPS, releasing large amounts of inflammatory mediators and proinflammatory cytokines such as IL-1β and TNF-α (37, 43).

Bacterial LPS have been reported to have a significant effect on insulin sensitivity (5). Periodontitis may initiate or propagate insulin resistance by LPS-induced activation of IL-6 and TNF-α (31, 46, 55). Elevated levels of lL-1β are known to deplete cellular energy and to activate protein kinase C leading to pancreatic β-cell destruction through apoptosis (56). TNF-α has been implicated as a causative factor in insulin resistance and T2DM in animal models and in human studies. Elevated levels of TNF-α inhibit tyrosine kinase activities of the insulin receptor and reduce synthesis of the insulin-responsive glucose transporter, leading to an insulin resistance (11). All these findings suggest that proinflammatory cytokines, such as lL-1β and TNF-α, produced as a systemic response to periodontal infection, are responsible for insulin resistance and subsequent poor glycemic control in periodontitis patients. Monocytes play an important role in periodontal tissue breakdown and patients with periodontitis have shown enhanced MCP-1 expression in the periodontal tissues (1). Elevated levels of MCP-1 levels have been reported in diabetic patients compared with healthy controls (26). Local and systemic hyper-responsiveness of these monocytes leads to increased TNF-α levels in gingival crevicular fluid (GCF) (3). Thus in individuals with T2DM and periodontitis, an elevated chronic systemic inflammatory state induced by periodontal disease may contribute to insulin resistance and worsen glycemic control (17).

Nonsurgical periodontal therapy that reduces circulating levels of TNF-α may help to restore insulin sensitivity, thereby improve glycemic control (30, 31). Recent evidences from studies of patients with both diabetes and periodontitis found that periodontal therapy can reduce circulating levels of TNF-α (21). In one of these studies (19), the reduction in serum levels of TNF-α was accompanied by, and strongly correlated with, a significant decrease in mean HbA1c values (from 8.0% to 7.1%). This suggests that a reduction in periodontal inflammatory mediators in the serum can improve glycemic control.

In the present meta-analysis, we pooled and analyzed data from 8 randomized controlled clinical trials exploring the effects of periodontal therapy on glycemic control in type 2 diabetic patients with periodontal diseases. Considering insufficient number of available randomized controlled trials being included in this meta-analysis, four different analyses were performed. The results of HbA1c meta-analysis suggested that periodontal treatment decreased HbA1c levels on average by 1.03% of 3-month duration, 1.17% of 6-month duration, and 1.21% of all duration combined (3, 6 and 9 months) compared with no periodontal treatment in type 2 diabetic patients with periodontitis. The magnitude of difference in HbA1c levels after periodontal therapy from our analysis is in line with those reported in previous systematic reviews and meta-analyses on the effecta of periodontal therapy on glycemic control (20, 50). However, the results of FPG meta-analysis revealed that periodontal treatment resulted in a non-significant reduction in FPG levels at the end of 3 months compared with no periodontal treatment in type 2 diabetic patients with periodontal diseases.

Several intervention studies, systematic reviews and meta-analyses report the effects of periodontal therapy on glycemic control, but the periods of treatment still remain inconsistent due to the wide variety of study designs, inadequate sample sizes, populations recruited, and combined enrolment of patients with type 1 diabetes (T1DM) and T2DM. In our analysis, we selected only randomized controlled trials, and restricted to type 2 diabetic patients, because we observed an upward trend of periodontal diseases in older type 2 diabetic patients. We observed intervention results for 3 and 6 months and conducted separate and integrated meta-analyses because of the low number of trials enrolled.

There are several limitations in the present meta-analysis. Significant heterogeneity was observed among the enrolled trials. However, a comprehensive evaluation of the sources of heterogeneity was impossible because the baseline characteristics of some studies were not available. The number of available studies is relatively small, with a limited number of samples. Some potentially relevant studies were excluded from the analyses because HbA1c data were not reported. The use of systemic or local antibiotics (15, 38, 48) as an adjunct therapy to basic periodontal treatment in some studies caused confusions on the effectiveness of intervention methods. Periodontal treatment should improve periodontal health. However, there are no adequate studies reporting outcomes of periodontal intervention. Meta-analysis is essentially an observational study as a limitation, and some biases are inevitable. This affects the strength of argument and extrapolation of conclusions of meta-analysis to a certain extent. Hence, we propose more large-sample, randomized controlled, blinded, clinical intervention trials of diabetic patients with periodontal diseases. Study duration should be more than 6 months. Furthermore, we suggest that plasma inflammatory markers should be measured as outcome indicators in addition to glucose metabolism and periodontal indicators.

In conclusion, our meta-analysis revealed that periodontal treatment could decrease HbA1c levels of type 2 diabetic patients with periodontal diseases, and improve glycemic control of type 2 diabetic patients with periodontal diseases. These results further support the notion that all healthcare professionals should aim to promote oral health in patients with diabetes not only to reduce the burden of oral diseases and prevent tooth losses, but potentially contributing to better glucose management.

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