Effect of Periodontal Treatment on Glycemic Control of Diabetic Patients

A systematic review and meta-analysis

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OBJECTIVE — There is growing evidence that periodontitis may affect general health. This study was assigned to explore the robustness of observations that periodontal therapy leads to the improvement of glycemic control in diabetic patients.

RESEARCH DESIGN AND METHODS — A literature search (until March 2009) was carried out using two databases (MEDLINE and the Cochrane Library) with language restriction to English. Selection of publications was based on 1) original investigations, 2) controlled periodontal intervention studies where the diabetic control group received no periodontal treatment, and 3) study duration of ≥3 months.

RESULTS — Screening of the initial 639 identified studies and reference checking resulted in five suitable articles. A total of 371 patients were included in this analysis with periodontitis as predictor and the actual absolute change in A1C (ΔA1C) as the outcome. The duration of follow-up was 3–9 months. All studies described a research population of type 2 diabetic patients in whom glycemic control improved after periodontal therapy compared with the control group (range ΔA1C: Δ = −1.17 up to Δ = −0.05%). The studies in a meta-analysis demonstrated a weighted mean difference of ΔA1C before and after therapy of −0.40% (95% CI = −0.77 to −0.04%, P = 0.03) favoring periodontal intervention in type 2 diabetic patients. Nevertheless, this improvement in %A1C must be interpreted with care due to limited robustness as evidenced by heterogeneity among studies (59.5%, P = 0.04).

CONCLUSIONS — The present meta-analysis suggests that periodontal treatment leads to an improvement of glycemic control in type 2 diabetic patients for at least 3 months.

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Periodontitis is a chronic multifactorial infectious disease of the supporting tissues of the teeth (1). It is estimated that between 10 and 15% of adults from 21 to 50 years of age and about 30% of subjects >50 years of age have severe periodontitis (2,3). Clinically, patients suffer from gradual loss of tooth attachment in the alveolar bone leading to periodontal pockets, receding gums, loose teeth, and eventually tooth exfoliation, which may result in changes in diversity of food uptake, possibly affecting general health (4). Often gums are red and swollen, bleed easily, and patients with periodontitis suffer from bad breath.

Treatment of periodontitis includes mechanical removal of supra- and subgingival bacterial plaque with scalers, curettes or ultrasonic devices (scaling and root planing [SRP]), and intensive oral hygiene instructions for the patient. A close to ideal oral hygiene regimen is the only way to prevent formation of new dental plaque deposits and re-infection of the subgingival tissues. The routine use of systemic or local antibiotics as an adjunctive therapy to SRP is still controversial in terms of improvement of clinical periodontal status (5–7). Surgery regularly is needed to reduce or eliminate deep residual periodontal lesions.

Diabetes and periodontal disease are two chronic diseases that have long been considered to be biologically linked. A large amount of case reports, cross-sectional studies, longitudinal studies, and reviews report the adverse effects of diabetes on the onset, progression, and severity of periodontitis (8,9). The prevalence of periodontitis in diabetic subjects is estimated to be double or even triple the number in the normal population (10). It has been suggested that hyperglycemia and resultant advanced glycation end product formation, which is one of the several pathways that is thought to lead to the classic microvascular and macrovascular complications of diabetes, are also involved in the pathophysiology of periodontitis in diabetic subjects (8).

There is a growing body of evidence supporting the fact that the periodontal infection with gram-negative microorganisms (11,12) adversely affects glycemic control (9,13). Thus, it is now acknowledged that due to untreated or inadequately controlled moderate-to-severe periodontitis, the systemic inflammatory burden may be increased. For example, in periodontitis patients without other apparent diseases, C-reactive protein (CRP) levels are higher compared to subjects without periodontitis (14). Similarly, it has been suggested that a microbiological imbalance in the gut may increase the gram-negative bacterial load, which, through lipopolysaccharides leakage into the circulation, also increases the systemic inflammatory burden. The increased inflammation eventually triggers insulin resistance (15,16).

More direct evidence regarding the effects of periodontal disease on glycemic control of diabetic patients comes from intervention studies using periodontal therapy. Since the beginning of the 1990s, several studies have investigated the association between periodontal therapy and...
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the improvement of glycemic control in diabetic patients. For example, Iwamoto et al. (17) showed that periodontal treatment in type 2 diabetic patients is effective in improving metabolic control. However, the latter and many other studies are uncontrolled, provide conflicting data, and report short-term results (<3 months). Because of the chronic nature of the development, progression, and severity of complications in diabetic patients, only longer-term results of periodontal treatment are meaningful. Therefore, we put the hypothesis forward that if periodontitis is causally related to the worsening of parameters of diabetic patients, then periodontal treatment should improve glycemic control.

Our aim was to perform a systematic review of intervention studies to answer the question of whether periodontal treatment affects the general health of diabetic patients by improving glycemic control compared with no periodontal treatment after at least 3-month follow-up.

RESEARCH DESIGN AND METHODS

Search strategy

Two databases, MEDLINE (via PubMed) and the entire Cochrane Library, have been searched using free-text search terms and the boolean operators “OR” and “AND”. “[Periodontal disease” OR periodontitis OR “periodontal infection” OR periodont*] AND [“diabetes” OR diabet* OR diabetic* OR “diabetic patient*” OR “diabetes patient*” OR “non insulin dependent diabetes” OR niddm OR “insulin dependent diabetes” OR iddm OR “type 1 diabetes” OR t1dm OR “type 2 diabetes” OR t2dm] AND [therapy OR treatment OR intervention] from January 1960 to 31 March 2009. Additional searches were conducted in MEDLINE’s and Cochrane’s medical subject headings with: [Periododontal diseases] AND [Diabetes Mellitus] AND [Therapeutics OR Therapy OR Intervention studies].

In addition, the reference lists of articles, which were obtained by the electronic search, were searched manually for relevant articles. The language of the studies in the literature search was restricted to English.

Study selection criteria

To be included in the systematic review, studies had to meet the following criteria: 1) original investigations; 2) intervention studies containing diabetic patients with periodontitis receiving periodontal treatment and diabetic patients with periodontitis receiving no periodontal treatment (controlled clinical trial [CCT] or randomized clinical trial [RCT] design) and outcomes related to metabolic control; 3) studies with a study duration of ≥3 months; and 4) studies conducted within a human population.

With the help of these inclusion criteria, the title and abstract of all the articles in the electronic search were evaluated on relevance. From the selected articles, the full texts were reviewed, followed by a decision on their eligibility for inclusion.

Methodological study quality assessment

For RCTs and CCTs, the following parameters were investigated (standard assessment form developed by the Dutch Cochrane Centre and the Dutch Institute for Healthcare Improvement CBO [http://www.cochrane.nl/nl/newPage1.html]): 1) allocation concealment, 2) randomization, 3) blindness of examiner and/or patient, and 4) loss to follow-up.

Data extraction and statistical analysis

From all relevant studies, the main features that were extracted were 1) characteristics of the population (i.e., age, sex, country of birth, extent), 2) definition of diabetes (i.e., type, duration, metabolic control), 3) definition of periodontitis, and 4) intervention (i.e., type, duration), study duration, outcome, and study design.

All suitable data for a meta-analysis were entered and analyzed with RevMan 4.2 (http://www.cc-ims.net/RevMan). A meta-analysis was conducted for RCTs and CCTs in which the intervention group received SRP (with or without adjunctive antimicrobial therapy), and the control group received no periodontal therapy. The absolute difference (Δ) in %A1C for baseline-end, if not reported in the article, was calculated for the intervention and the control groups by means of the formula:

\[
\Delta \text{%A1C ti} = \text{%A1C ti 1} - \text{%A1C ti 2},
\]

where %A1C ti 1 is the mean %A1C value before treatment and %A1C ti 2 is the mean %A1C after treatment. Again, if not reported, for some studies, the variance (and consequently SD) of Δ %A1C ti was estimated as follows (18):

\[
S ti^2 = S ti 1^2 + S ti 2^2 - 2r \cdot S ti 1 \cdot S ti 2,
\]

where \( S ti^2 \) is the variance of \( \Delta \) in %A1C levels, \( S ti 1^2 \) is the variance of the mean baseline %A1C values, \( S ti 2^2 \) is the variance of the mean end %A1C value, \( r \) is the correlation between the baseline and end values, and \( S ti 1 \) and \( S ti 2 \) are the SDs of the baseline and end values, respectively. We assumed \( r \) to be 0.5 as was previously described (19).

For each meta-analysis, the weighted mean difference (WMD) was calculated, nested in a random-effects model with corresponding Z statistics, P values, and 95% CIs. Also, a test for heterogeneity was performed. For this test, the I² statistic describes the proportion of total variation due to heterogeneity where 0% indicates no heterogeneity and 100% indicates maximal heterogeneity among the studies included in the meta-analysis (20). Heterogeneity indicates the robustness of the WMD. The results of the meta-analysis are presented in a forest plot with the following indicators 1) the raw data (means and SDs) for each arm per included study; 2) point estimates and CIs for the chosen effect measure, as blocks and lines, respectively; 3) heterogeneity statistic (I²); 4) the total number of participants per group; 5) the overall average effect (WMD and Z statistics) in a random-effects model; and 6) percent weight given to each study.

RESULTS — The combined MEDLINE (via PubMed) and the Cochrane Central searches resulted in 639 potentially eligible articles (Fig. 1). These articles were screened by title and abstract for relevance. The screening resulted in 74 articles that qualified for full-text reading. After full-text reading, 40 articles were deemed unsuitable and were therefore excluded (supplemental Table 1A and C, which is available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1378/DC1). Screening of the reviews (n = 29) (supplemental Table 1B) for unpublished data did not provide any additional articles. Supplemental Table 1C presents the excluded intervention studies (n = 35) and the main reason for exclusion. Five articles (three RCTs and two CCTs) fulfilled the inclusion criteria and were processed for data extraction (Table 1) (21–25).

General characteristics

From the five included studies, two were performed in North America (the U.S.) (21,25), two were performed in Asia
(Japan [22] and Thailand [24]), and one was performed in the Middle East (Turkey) (23). The study duration ranged from 3 to 9 months. All studies described a study population having type 2 diabetes and suffering from periodontitis. In total, 199 patients (range 22–82 patients per study) were in the intervention group and 183 patients (range 17–83 patients per study) were in the control group. The mean age per study ranged from 56 to 62 years for the intervention group and from 53 to 67 years for the control group. In addition, the baseline A1C levels per study ranged from 7.2 to 9.9% for the intervention group, whereas the baseline A1C levels for the control group ranged from 6.9 to 10.2%.

All subjects in the intervention group received SRP with (21,22,24) or without (23,25) local or systemic administration of antibiotics, whereas no subject of the control group received any form of periodontal intervention.

### Periodontal intervention and A1C

All studies reported absolute changes (Δ) in A1C as parameter of metabolic control. Four of the five studies reported mean differences between baseline and end of trial with or without SDs (21,23–25). One study (22) reported changes of A1C levels graphically; the mean values and SDs were obtained through e-mail communication with the authors. Two of the five studies showed a significant improvement in metabolic control after periodontal therapy as measured by a significant decrease in A1C levels compared with that in the untreated control group (I-C Δ<sub>1.17%</sub> [23], I-C Δ<sub>1.10%</sub> [25]). Katagiri et al. (22), Jones et al. (21), and Promsudthi et al. (24) also showed a decrease in A1C levels after periodontal therapy (I-C Δ<sub>-0.05%</sub>, I-C Δ<sub>-0.16%</sub>, and I-C Δ<sub>-0.31%</sub>, respectively); however, these decreases were reported to be not significant. A multiple regression analysis in the study by Katagiri et al. (22) for significant variables associated with changes of A1C levels between baseline and 6 months showed that the A1C decrease correlated with decreases in high-sensitivity CRP (hs-CRP) levels after periodontal treatment (P = 0.03) (22). Based on this analysis, Katagiri et al. (22) divided the intervention group into CRP-decreased and CRP-unchanged groups. This subanalysis showed that A1C levels decreased significantly in the CRP-decreased group compared with baseline levels, but not in the CRP-unchanged group.

### Periodontal intervention and other parameters of glycemic control

Three studies also reported change in fasting plasma glucose (FPG) as parameter of metabolic control, and two studies showed a nonsignificant decrease in FPG after periodontal treatment compared with that in the control group (I-C Δ=−5.18 mg/dl [23], I-C Δ=−3.83 mg/dl [24]). Notably, Katagiri et al. (22) showed a nonsignificant deterioration of metabolic control as reflected by a nonsignificant increase in FPG after periodontal treatment compared with that in the control group (I-C Δ=22 mg/dl). In addition, Kiran et al. (23) showed a significant decrease of 2-h postprandial glucose (PPG) levels after periodontal therapy compared with baseline levels of the treatment group (I<sub>end of trial</sub>−I<sub>baseline</sub> Δ=23.6 mg/dl, P = 0.027). However, compared with that in the control group, the decrease in 2-h PPG levels was not significant (I-C Δ=−25.1 mg/dl, P = 0.067).

### Meta-analysis

The effect of periodontal treatment on A1C levels (five studies) and FPG levels (three studies) could be analyzed from the available intervention studies (Fig. 2A and B). The range of A1C mean differences between baseline and end for the treatment groups was −1.90 to −0.14%, whereas the untreated individuals showed a range of −0.80 to 0.31%. The WMD of A1C mean differences baseline to end between treatment groups and control groups was −0.40% (95% CI −0.04 to −0.77%) (test of the overall effect, P = 0.03). The heterogeneity (P²) be-

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**Figure 1**—Flow chart outlining the search strategy and results along various steps.
Table 1—Included treatment studies reporting study characteristics, definition of periodontal disease, definition of diabetes, results, and quality assessment in reverse chronological order

| Author(s) | Population | Definition of periodontal disease (inclusion criteria) | Definition of diabetes (inclusion criteria; baseline A1C levels; diabetes duration) | Intervention | Study duration (observation points) | Outcome | Number of included patients (men) | Results | Quality* |
|-----------|------------|------------------------------------------------------|--------------------------------------------------------------------------------|-------------|-------------------------------------|---------|----------------------------------|---------|---------|
| Katagiri et al. 2009 (22) | Diabetic patients with periodontitis (mean age 1: 60.3 ± 9.9 years; C: 59.0 ± 4.8 years) at five diabetic clinics in four cities: Tokyo, Kagoshima, Aichi, and Kyoto (Japan) | Total ≥11 teeth ≥2 sites with PPD ≥4 mm | Inclusion criteria: Type 2 diabetes with A1C value between 6.5 and 10.0% | SRP + topical administration of 10 mg minocycline ointment in every periodontal pocket. C: Oral hygiene instructions | 6 months (1, 3, and 6 months) | A1C | 32 (NR) C: 17 (NR) | -A1C | + |
| | | | Baseline % A1C: I: 7.2 ± 0.9 C: 6.9 ± 0.9 | Duration (years): I: 1.13 ± 0.6 C: 8.8 ± 7.5 | | | | | |
| Jones et al. 2007 (21) | Diabetic patients with periodontitis (mean age 1: 59 years; C: 60 years) at four VA facilities: Boston, MA | Total ≥8 teeth -ChTN score ≥3 in ≥2 sextants | Inclusion criteria: Type 2 diabetes with ≥1 A1C value of ≥8.5% in the last 6 months and a baseline A1C value of ≥8.5% | SRP + doxycycline (100 mg/day for 14 days) + CHX rinses (0.12%, twice daily for 4 months) | 4 months (0 and 4 months) | A1C | 82 (82) C: 83 (78) | -A1C | + |
| | | | Baseline % A1C: I: 9.9 C: 10.2 | Duration (years): I: 1.14 C: 14.1 | | | | | |
| Kiran et al. 2005 (23) | Diabetic patients with periodontitis (mean age 1: 55.95 ± 11.21 years; C: 52.82 ± 12.27 years) from the Faculty of Medicine: Department of Metabolic Diseases & Endocrinology, Ankara University, Turkey | NR | Inclusion criteria: Type 2 diabetes with A1C value between 6 and 8% | SRP | 3 months (0 and 3 months) | A1C | 22 (10) C: 22 (8) | -A1C | + |
| | | | Baseline % A1C: I: 7.31 ± 0.74 C: 7.06 ± 0.72 | Duration (years): I: 9.32 ± 8.36 C: 8.05 ± 9.90 | | | | | |
| Promsudthi et al. 2005 (24) | Diabetic patients with periodontitis (mean age 1: 61.1 ± 5.83 years; C: 61.6 ± 5.81 years) at the Diabetic Clinic of Rajavithi Hospital, Bangkok, Thailand | Total ≥14 teeth with ≥8 sites with PPD ≥5 mm and CAL ≥5 mm | Inclusion criteria: Type 2 diabetes with A1C values between 7.5 and 11.0% | SRP + doxycycline (100 mg/day for 14 days) | 3 months (0 and 3 months) | A1C | 17 (11) C: 25 (8) | -A1C | +/- |
| | | | Baseline % A1C: I: 8.98 ± 0.88 C: 9.17 ± 1.02 | Duration (years): I: 8.30 ± 4.21 C: 14.30 ± 7.57 | | | | | |

*Quality assessment: +: High, +/-: Moderate, -: Low
The range of FPG mean differences between baseline and end for the treatment groups was −3.63 to 19.00 mg/dl, whereas the untreated individuals showed a range of −3.00 to 1.22 mg/dl. The WMD of mean FPG differences baseline-end between treatment groups and control groups was 2.30 mg/dl (95% CI −13.64 to 18.24 mg/dl) (test of the overall effect, P = 0.78). The heterogeneity (I²) between the three studies was 23.7% (P = 0.27) (Fig. 2B).

**CONCLUSIONS** — The current review provides the most accurate reflection of available literature to date to answer the question of whether periodontal treatment affects the general health of type 2 diabetic patients by improving glycemic control compared to no periodontal treatment after at least 3-month follow-up. Although previous systematic reviews on this topic (5,26) were conducted, we believe that the current inclusion criteria of available studies result in a better understanding of the effect of periodontal treatment on diabetic patients for the following reasons: 1) We included only studies with at least 3-month follow-up. A1C is a reflection of the mean blood glucose concentration over the preceding 1–3 months and a difference over a shorter period may be clinically less relevant (13). 2) We only used controlled studies in our analysis in which the control group with type 2 diabetes received no periodontal treatment to overcome the problem of a possible Hawthorne effect (22,23). 3) The calculation of WMD is the most suitable parameter for a proper meta-analysis (28) since back-transformation of a standardized mean difference (5) will lead to an overestimation of the total effect of periodontal therapy. Thus, we conclude from the current systematic review, based on strict inclusion criteria of literature, that periodontal therapy for type 2 diabetic patients with periodontitis is favorable and can reduce A1C levels on average by 0.40% more than in nonintervention control subjects.

**Changes in (blood) levels of markers, which reflect the metabolic regulation of diabetes**

Although only two of the five studies showed an improvement of metabolic control after periodontal treatment (23,25), the results of all studies combined in our meta-analysis suggest that periodontal treatment results in an absolute decrease of A1C of 0.40% compared with no periodontal treatment in type 2 diabetic patients. This decrease of A1C is also clinically relevant since any decrease of A1C will result in less diabetic complications (29,30).

Interestingly, the improvement in glucose metabolism, as evidenced by the reduction of %A1C, was not seen in FPG levels (Fig. 2B). However, FPG levels reflect the metabolic control at one time point and one moment of the day, whereas A1C reflects glucose metabolism over the preceding 1–3 months; this is also true for PPG levels.

The results of our A1C meta-analysis need to be viewed with caution for four main reasons: 1) The lack of robustness as revealed by the significant heterogeneity. Inadequate attention to heterogeneity may result in misinterpretation of the results (31). For example, there is only minor overlap of the CIs between the Kiran et al. (23) and Katagiri et al. (22) trials, suggesting that these studies are less comparable; differences in ethnicity and lifestyle factors may be a possible explanation. 2) The small number of studies (n = 5) with relative small study groups. There is a lack of large randomized controlled intervention trials in type 2 diabetic patients. 3) The shortcomings in study design of several studies. Two studies used groups with selection bias by placing treatment avoiders in the control group (24,25). Two other studies used metabolically controlled diabetic patients as determined by a %A1C of ≤7, possibly affecting improvement of metabolic control after periodontal treatment (22,23). Furthermore, the use of systemic or local antibiotics as an adjunctive therapy to basic periodontal treatment is possibly another factor of study design that may influence the outcome. It is interesting to note that the only two studies in our meta-analysis that showed a significant decrease in A1C levels after periodontal treatment did not use antibiotics as an adjunctive therapy (23,25), whereas the other studies did use antibiotics. The use of antibiotics is still controversial whether it is beneficial in terms of improvement of clinical periodontal status (5–7) or glycemic control (32,33). It is clear that further trials specifically addressing this adjunctive form of periodontal therapy are needed. 4) The lack of an instrument to quantify periodontal inflammation for all studies. Inflammation is associated with the onset and progression of diabetes.

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**Table 1—Continued**

| Study | Definition of diabetes (inclusion criteria) | Number of included patients | Design (per group) | Outcome | Results | Quality* |
|-------|------------------------------------------|-----------------------------|-------------------|---------|---------|---------|
| Stewart et al. (23) | Diabetic patients with periapical radiolucencies and sufficient periodontal destruction | 2001 (25) | 18 months (months) | -A1C: baseline A1C levels | -A1C: intervention group | +/− |
| Angeles Outpatient Diabetic Clinic, Los Angeles, CA | No treatment. Nothing, nothing, nothing periodontal treatment | 2.30 mg/dl (95% CI 0.78–0.80) | +− | 0.02 | 0.001 |
| | NR, not reported | 0.06 |

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**Changes in (blood) levels of markers, which reflect the metabolic regulation of diabetes**

Although only two of the five studies showed an improvement of metabolic control after periodontal treatment (23,25), the results of all studies combined in our meta-analysis suggest that
Quantifying the amount of periodontal inflammation and possibly also quantifying the pathogenic bacterial load, together with the improvement of metabolic control, will give us more insight into the relation between periodontitis and diabetes. Most likely, treatment of the generalized severe form of periodontitis will be more beneficial in terms of glycemic control of diabetic patients than treatment of the localized moderate form of periodontitis. Recently, a new tool has been developed to quantify the inflammatory burden of periodontitis (34) and showed that the amount of periodontal inflammation was related to A1C values of diabetic patients in a dose-responded way (35). Regarding the relation between systemic inflammatory burden and diabetes, one study (22) reported the effect of periodontal treatment on hs-CRP blood levels in diabetic patients. The authors revealed in a multiple regression analysis of all subjects that Δhs-CRP levels at 1 month after periodontal treatment correlated significantly with the reduction of A1C at 6 months after periodontal treatment. It suggests that change in hs-CRP level is a factor related to the change in A1C level. However, this study did not use an untreated control group and therefore was not included in the current systematic review.

We have shown that periodontal treatment leads to improvement of the general health of type 2 diabetic patients by affecting the metabolic control: after periodontal treatment, A1C can be significantly reduced by absolute 0.40% based on RCTs and CCTs with at least 3-month follow-up. However, more evidence is needed as is reflected by a wide CI. More homogeneous evidence is needed as is reflected by a significant heterogeneity (0.59%) among the studies. We propose further trials to be initiated as follows (40):

- A large single-blind randomized controlled study of diabetic patients with moderate or severe periodontitis.
- The treatment group to receive basic periodontal treatment (oral hygiene instruction and SRP), whereas the control group not to receive any form of periodontal treatment.
- Follow-up period ≥6 months.
- Sample size is large enough to analyze patients with moderate and severe periodontitis separately.
- Outcome:
  - Change in (plasma) markers of glycemic control.
  - Change in the amount of periodontal inflammation.
  - Change in (plasma) markers of systemic inflammation.

ADDENDUM — No new studies according to the inclusion criteria of this article have appeared in the literature as of the time of the production of this article (November 2009).

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