TITLE: Treatment of Periodontal Disease in Patients with Diabetes: A Review of Clinical and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

Periodontal disease refers to any inherited or acquired disorder that affects the tissues supporting the teeth (periodontium). The most common form of periodontal disease is gingivitis which is the result of inflammation of the gums (gingiva). If left untreated, gingivitis may progress to periodontitis where pockets and crevices form between the gingiva and the root of the tooth. The formation of periodontal pockets is associated with inflammation and damage in the tissues that comprise the periodontium. Severe periodontitis is associated with pain, discomfort, impaired mastication, tooth loosening, and eventual tooth loss. The primary treatment strategy for periodontitis is scaling and root planning, a non-surgical procedure used to remove dental plaque and calculus from the crown and root of the tooth. Special attention is given to the debridement of bacterial biofilm present in periodontal pockets.¹

Cross-sectional and prospective cohort studies have demonstrated that patients with diabetes mellitus have a higher prevalence and more severe forms of periodontal disease than patients without diabetes.¹² This association has resulted in suggestions that periodontal disease is a microvascular complication of diabetes.³ There is uncertainty regarding the effect of treating periodontal disease on glycemic control or diabetes-related complications in patients with diabetes mellitus. This report will review the clinical effectiveness and cost-effectiveness of treating periodontal disease in patients with type 1 or type 2 diabetes mellitus.

RESEARCH QUESTIONS:

1. What is the evidence that the treatment of periodontal disease in patients with diabetes mellitus reduces diabetes-related complications and improves glycemic control?

2. What is the cost-effectiveness of treatment of periodontal disease in patients with diabetes mellitus?
METHODS:

A limited literature search was conducted on key health technology assessment resources, including OVID’s Medline and Embase, PubMed, the Cochrane Library (Issue 5, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and May 17, 2010. No filters were applied to limit the retrieval by study type. Internet links were provided, where available.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs), controlled clinical trials, and economic evaluations.

SUMMARY OF FINDINGS:

Four systematic reviews and meta-analyses were included in this review. Six RCTs, one controlled clinical trial, and one economic evaluation were identified in the literature search. Of these studies, five RCTs and the controlled clinical trial were summarized in the systematic reviews and, therefore, are not reviewed separately. The remaining RCT was not included in any of the systematic reviews as their literature searches did not include databases where this particular journal is indexed or predated publication of this study. None of the included systematic reviews addressed the cost-effectiveness of periodontal treatment in patients with diabetes. There were no health technology assessments identified in the literature review. The protocol for an on-going RCT is presented in the appendix.

Systematic reviews and meta-analyses

A recent meta-analysis of RCTs (2010) assessed the effect of periodontal therapy on glycemic control in patients with type 1 or type 2 diabetes. A systematic review was performed to identify RCTs published up to March 2010. The literature search was comprehensive involving multiple databases, hand-searching, grey-literature, and was conducted without language restrictions. RCTs were selected for inclusion if they involved: 1) patients at least 16 years of age with a diagnosis of type 1 or type 2 diabetes and periodontitis; 2) a minimum post-treatment follow-up of 90 days; 3) a comparison of one or more periodontal interventions with no treatment or another active intervention; and 4) reported change in hemoglobin A1C (HbA1C). Continuous data were pooled where the authors deemed studies were sufficiently homogeneous. Overall, this systematic review was conducted according to a protocol designed using a rigorous methodology involving duplicate study selection, data extraction, and quality assessment. The internal validity of the included RCTs was assessed using a validated methodology. The authors reported that a majority of studies failed to provide methods for randomization, allocation concealment, and blinding. Furthermore, the majority of trials failed to adequately describe patient disposition and the process for handling missing data.

A total of seven RCTs involving 512 patients (range: 35-193) were included in the review; three of the RCTs compared an intervention with no intervention. These three RCTs (n = 244) compared scaling, root planning, and oral hygiene (with or without
antibiotics) against no treatment or usual treatment (i.e., the patients' normal dental care routine). The data from these trials were pooled using fixed-effects meta-analysis and the results demonstrated a statistically significant reduction in HbA1C favouring the active treatment regimen [weighted mean difference (WMD) -0.40%; 95% confidence interval (CI) -0.78%, -0.01%]). This finding should be interpreted with caution as there is considerable clinical and methodological heterogeneity between these three RCTs, particularly with regard to the usage of antibiotics. Subgroup analyses were performed to investigate this heterogeneity; however, the statistical power of these is limited as each trial used a different antibiotic strategy. When separated according to antibiotic usage the results were not statistically significant for trials without adjunctive antibiotics (p = 0.09), with adjunctive antibiotics in the test group (p = 0.14), and with antibiotics in both test and control groups (p = 0.74). There is also considerable between study heterogeneity with regard to baseline HbA1C (range 7.2-10.1%), an important limitation given that HbA1C is the primary outcome for this review. The authors concluded that the treatment of periodontal disease has statistically significant and clinically meaningful beneficial effects on glycemic control; however, they acknowledge that the few RCTs available were inadequately powered to detect meaningful treatment effects on glycemic control. With regard to the observed reduction in HbA1C achieving clinical significance, there is no universally accepted minimal clinically important difference in HbA1C. Commonly cited MCIDs typically range from -0.5 to -1.0%; therefore, the reduction of -0.4% observed with periodontal treatment is lower relative to other interventions used to control hyperglycemia.

Teeuws et al (2010) conducted a systematic review and meta-analysis of RCTs and controlled clinical trials that assessed the effect of periodontal therapy on glycemic control in patients with diabetes. A literature search was performed from January 1960 to March 31, 2009 using two databases and restricted to English language publications. Articles meeting the following criteria were selected for inclusion: 1) original investigation; 2) controlled periodontal intervention studies involving human patients with diabetes and where the control group received no periodontal treatment; 3) a study duration of at least three months; and 4) reported outcomes related to glycemic control. The internal validity of the included studies was assessed based on methods for allocation concealment, randomization, blinding, and loss to follow-up. A meta-analysis was performed for all RCTs and controlled clinical trials that compared scaling and root planing (with or without antibiotics) against no periodontal therapy. Potential limitations with this systematic review include the failure to specify whether or not the study was conducted according to a protocol designed a priori and uncertainty concerning the use of duplicate reviewers.

A total of five studies (N = 382) were included in the review (three RCTs and two controlled clinical trials). These five trials were pooled and the results demonstrated a statistically significant reduction in HbA1C in patients that received periodontal treatment in comparison with those that did not (WMD -0.40%; 95% CI: -0.04%, -0.77%). A second meta-analysis was performed to assess the impact of periodontal treatment on the change from baseline in fasting plasma glucose (FPG). Three studies were pooled and the differences in FPG between treatment groups and control groups were not statistically significant (WMD: 2.30 mg/dl; 95% CI: -13.64, 18.24 mg/dl). The I² values were 59.5% and 23.7% for the HbA1C and FPG meta-analyses, respectively. This indicates a moderate level of inconsistency in the results for HbA1C; however, there were no sensitivity analyses conducted to explore the underlying reasons for this statistical heterogeneity.
The authors concluded that periodontal therapy can reduce HbA1C levels on average by 0.40% in patients with type 2 diabetes and periodontitis. However, there are important differences in the methods and clinical characteristics of the trials included in this meta-analysis, hence the results need to be interpreted with caution. The results were derived from a small number of studies (n = 5) with low statistical power that involved different procedures for patient allocation (i.e., randomized versus non-randomized). Teeuws et al, also note that the non-randomized studies placed treatment avoiders in the control group, thus increasing the likelihood of selection bias. Finally, there was variability in the baseline characteristics of patients for HbA1C and severity of periodontal disease, in the treatment regimens (with or without antibiotics), and in the length of follow-up (range: 3 to 18 months).

Darré et al (2008) conducted a systematic review and meta-analysis of intervention studies investigating the effect of periodontal treatment on glycemic control. A literature review was conducted from January 1976 to December 2007 for articles meeting the following criteria: 1) report the results of an intervention (randomized or non-randomized); 2) involved patients with a diagnosis of diabetes and periodontitis; and 3) reported a numerical value for HbA1C. The literature search was comprehensive involving multiple databases, hand-searching, grey-literature, and was conducted without language restrictions. The review included both controlled and uncontrolled clinical trials; however, only data from the controlled trials were included in the meta-analysis. Sensitivity analyses were conducted to explore heterogeneity with regard to the type of diabetes, age of participants, duration of the trial, type of periodontal intervention, and study quality. Data were pooled using fixed and random-effects meta-analysis. Overall, this systematic review was conducted using a rigorous methodology involving duplicate study selection and data extraction. The internal validity of the controlled trials was assessed in duplicate using CONSORT\textsuperscript{29} and Delphi criteria.\textsuperscript{30}

A total of 25 studies (N = 976) were included in the review of which 16 were uncontrolled (n = 491) and nine were controlled clinical trials (n = 485). The primary intervention in all 25 studies was full-mouth scaling and root planning, with some adding local or systemic administration of antimicrobials and/or the use of antiseptic mouth washes. The nine controlled trials were pooled and resulted in a statistically significant improvement in HbA1C [standardized mean difference (SMD): 0.46 (95% CI: 0.89, 0.11)]. The authors converted the SMD into a measure of change in HbA1C, and reported that periodontal treatment could result in a reduction in HbA1C of 0.79% (95% CI: 0.19, 1.40). Teeuw et al (2010) criticized this approach and suggested that back-transformation of SMD would lead to an overestimation of the effect size and that WMD is a more suitable parameter in this type of meta-analysis.\textsuperscript{7} A sensitivity analysis was performed by removing the study with the largest effect size and the overall effect was no longer statistically significant. The authors reported that there was no significant statistical heterogeneity and thus did not explore heterogeneity beyond removal of the trial with the largest effect size.\textsuperscript{28} There is substantial between-study clinical and methodological heterogeneity that should be taken into consideration when interpreting these findings. Similar to the review by Simpson et al (2008),\textsuperscript{4} the trials differed with respect to whether or not participants received antibiotics and/or antiseptic mouthwash in addition to scaling and root planning. Furthermore, there was variability in the duration of trials (range: 9-43.5 weeks), baseline HbA1C (range 7.0-10.4), and methods for measuring HbA1C. The authors concluded that, although their results suggest that treatment of periodontal disease in patients with diabetes may improve their glycemic control, the available evidence is too limited to make clinical recommendations.
A systematic review and meta-analysis by Janket et al. (2005) assessed the effect of periodontal therapy on glycemic control in patients with diabetes. A systematic review was conducted from January 1980 to January 2005 for English language articles meeting the following criteria: 1) report the results of an intervention where causal inference can be made (randomized or non-randomized); 2) reported glycemic control as a primary or secondary outcome; and 3) were at least 2 months in duration. Continuous data were pooled using random-effects meta-analysis with sensitivity analyses and meta-regressions used to investigate differences in diabetes type, design of control group (i.e., self-control or parallel-group), and treatment modality (i.e., non-surgical debridement or antibiotics administration). It is unclear if the review was conducted according to a protocol designed a priori. Overall, this systematic review was conducted using a rigorous and well-reported methodology.

A total of 10 studies involving 456 patients with type 1 or type 2 diabetes met the inclusion criteria for this review. These studies are heterogeneous with regard to number of important clinical and methodological characteristics including: type of diabetes, study design (i.e., RCTs, controlled clinical trials, and interrupted time series), interventions (surgical, non-surgical, antibiotics, and oral disinfectants), and duration of trial (range: 2-12 months). Despite this heterogeneity, the authors pooled all ten intervention studies and reported a non-significant reduction in HbA1C following treatment for periodontitis (WMD -0.4%; 95% CI -1.5, 0.7). Subgroup analyses were presented for studies involving only patients with type 2 diabetes (WMD -0.7%; 95% CI -2.2, 0.9), only studies that used non-surgical debridement (WMD -0.4%; 95% CI -2.1, 1.3), and studies that used an antimicrobial intervention in patients with type 2 diabetes (WMD -0.7%; 95% CI -2.3, 0.9). The authors reported that there was insufficient evidence to conclude that treatment of periodontal disease has an effect on glycemic control in patients with diabetes.

**Randomized controlled trials**

Six RCTs were identified in the literature; however, five were summarized in the included systematic reviews. The additional study was a small RCT (n = 45) conducted in India which compared the following three treatments in patients with type 2 diabetes and moderate to advanced periodontitis: full mouth scaling and root planing only (group A); full mouth scaling and root planing followed by 100 mg systemic doxycycline for 14 days (group B); and no treatment (group C). The outcomes of interest for this RCT included HbA1C, post-prandial blood glucose (PPBG), and fasting blood glucose (FBG). Parameters of glycemic control were measured at baseline and at the end of three months. The change from baseline in HbA1C was -0.6%, -0.7%, and 0.06% for groups A, B, and C, respectively. The authors reported that the improvement in HbA1C observed in group A and group B were statistically significant in comparison with group C (p < 0.05). The change from baseline in FBG was not statistically significant for any of the three treatment groups. The authors reported a statistically significant reduction in 2 hour-PPBG for the treatment groups A and B and no significant change in the control group C.

The key limitations of this RCT included failure to report methods for randomization and allocation concealment, open-label design, small sample size and correspondingly low statistical power, no description of patient disposition or the procedure for handling missing data, and relatively short duration (3 months). The three groups appeared to be comparable at baseline and aside from the intervention of interest, the three groups received equal treatment with regard to their diabetes (i.e., there were no changes in the medication or diet, and no additional
guidance for managing their diabetic). Overall, the findings of this RCT should be interpreted with caution as there are substantial limitations with the internal and external validity of this study.

**Controlled clinical trials**

One controlled clinical trial\textsuperscript{14} was identified in the literature review; however, this study is included in two systematic reviews\textsuperscript{7,46} and, therefore, is not reviewed separately.

**Economic evaluations**

A retrospective cohort study was conducted to assess the impact of periodontal treatment on changes in overall risk and medical expenditures for patients with diabetes mellitus, coronary artery disease, and cerebrovascular disease. A two year (January 1, 2001 to December 31, 2002) retrospective examination of patients who received concomitant and continuous medical and dental coverage in a preferred provider organization plan from a large insurance provider (Aetna, Inc.) was conducted. In total, 51,560 patients with diabetes were identified and classified according to the dental treatments they received during the two year period: treatment for periodontitis (n = 3829), treatment for gingivitis (n = 3403), dental maintenance services (i.e., examination and preventative treatment; n = 27,699), dental services (i.e., restorative, prosthetic, and surgical treatment; n = 1473), or had no dental treatment (n = 15,156). The total medical per member per month (PMPM) cost for each category was calculated, excluding the cost of dental treatments. The PMPM values were adjusted for higher medical expenditures occurring in patients with greater illness or more severe chronic conditions. The authors used retrospective risk scores to control for differences in the overall disease burden of each patient group. The risk scores were obtained from the insurance provider and are based on medical claims, pharmacy claims, and demographic data.

The authors reported that, when adjusted for health risk, the PMPM costs for patients with diabetes who received treatment for periodontitis were significantly greater than patients with diabetes who received treatment for gingivitis, underwent dental maintenance services, other dental services, or had no dental treatment (p < 0.001 for each). Similar results were reported for the unadjusted PMPM costs. The data set used in this analysis did not account for several important confounding factors such as smoking, socioeconomic status, severity, and overall burden of dental disease. In addition, the authors stated that caution should be used in generalizing their findings to the general population. The authors’ overall conclusion was that it may be reasonable to recommend oral cavity examinations be included in guidelines for patients with diabetes.

**Limitations**

The four systematic reviews included in this report differed in their inclusion criteria, methods of critical appraisal, and approach to pooling data. As a result, there was variability with regard to whether or not the periodontal intervention resulted in a statistical significant improvement in HbA\textsubscript{1C}. The individual RCTs that compared periodontal treatment with no treatment are limited by small sample sizes (mean n = 55), short duration (mean 16 weeks), and heterogeneous populations, interventions, and comparators. Furthermore, all the included studies assessed HbA\textsubscript{1C} as the primary outcome of interest. There were no trials identified that assessed the
effect of periodontal interventions on more clinically meaningful diabetes-related complications such as nephropathy or ischemic heart disease, or overall mortality of patients. The additional RCT identified was also limited by a small number of patients (n = 46), short duration (12 weeks), and problems with internal validity.

The one economic evaluation identified for the treatment of periodontal disease in patients with diabetes was based on a retrospective cohort involving medical and pharmacy claims incurred over a two year period. The findings of this study may not be generalizable to Canadians given that the cohort was derived from members of a large health insurance provider in the United States. Furthermore, the study failed to address important confounding factors such as smoking and socioeconomic status.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

Three meta-analyses of RCTs and controlled clinical trials reported a statistically significant reduction in HbA1C following treatment of periodontal disease, and one meta-analysis of controlled and uncontrolled clinical trials reported no significant difference. The meta-analysis of RCTs was restricted to comparisons of periodontal treatment versus no treatment and, therefore, represents the best available assessment of the effect of periodontal interventions on glycemic control. The statistically significant reduction in HbA1C of -0.4% is less than the commonly cited minimal clinically important differences in HbA1C (range -0.5 to -1.0%); therefore, the effect of periodontal treatment is lower than that observed with other interventions used to control hyperglycemia such as diet, exercise, oral antihyperglycemic agents, or insulins. Furthermore, the individual clinical trials that form the evidence base of these systematic reviews have low statistical power, are heterogeneous, and have poor internal validity. Given these limitations, the findings reported in these reviews may not be generalizable to the broader population of patients with diabetes and periodontal disease. Well-designed RCTs with adequate statistical power and a longer duration of follow-up are required to confirm the results of these systematic reviews.

There is a lack of cost-effectiveness evidence regarding the use of periodontal treatment in patients with diabetes. Further evaluations based on robust clinical data will be required in order to properly ascertain the long-term cost-effectiveness of periodontal interventions in patients with diabetes.

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APPENDIX: Protocol for an Ongoing RCT

A protocol for a relevant RCT was identified in the literature review. The DIAPERIO trial will involve 150 patients randomized (1:1) to receive immediate periodontal treatment or delayed treatment. The periodontal treatment will include full mouth non-surgical scaling and root planing, systemic antibiotherapy, local antiseptics (chlorhexidine 0.12%) and oral health instructions. The primary outcome of the DIAPERIO trial will be the difference in change of HbA1c between the two groups after the 13-weeks.