



Oral and General Health - Exploring the Connection

Research Review September 2009

Associations between Periodontal Disease and Diabetes Mellitus

PROFESSIONAL VERSION

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Introduction

Both diabetes and periodontal diseases are common chronic diseases in many parts of the world. This report will provide a description of the current state of the evidence supporting a bi-directional relationship between diabetes and periodontal disease. The bi-directional relationship is one in which we recognize the evidence has established diabetes adversely affects periodontal health and, while not yet unequivocal, the evidence suggests periodontal infection (or periodontal disease) adversely affects diabetes by contributing to poorer glycemic control, increasing the risk for certain diabetes complications, and possibly increasing the risk for the development of diabetes.

The report is organized to address the following three topics:

1. Adverse Effects of Diabetes on Periodontal Health
2. Adverse Effects of Periodontal Infection on Glycemic Control in Diabetes:
 - a. Treatment Studies
 - b. Observational Studies
3. Periodontal Infection and Development of Complications of Diabetes
4. Periodontal Infection and Development of Diabetes Mellitus.

The literature search strategy for this report involved collaboration with a medical librarian conducting electronic searches in MEDLINE and EMBASE. Initially, we identified a set of sentinel articles based on our knowledge of the literature, which formed the basis of each successive search strategy and suggested relevant Medical Subject Headings (MeSH) and textual keywords for the search. Search terms included periodontal disease concepts (such as the exploded MeSH terms *periodontal diseases*, *peridontium*, and *periodontics*, and the truncated keyword *periodont**), diabetes concepts (such as the exploded MeSH terms *diabetes mellitus* and *diabetes insipidus*, and the keyword variants *diabet**, *dm 1*, *dm i*, *dm 2*, and *dm ii*), and other peripherally related diabetes concepts (such as the MeSH terms *Hemoglobin A Glycosylated*, *Blood Glucose*, *hyperglycemia*, and *hypoglycemia*, and the textual keywords *blood sugar*, *blood glucose*, *a1c*, *hb a1c*, *hba1c*, *sugar level*, *sugar control*, *glucose level*, *glucose control*, and *hyperglyc** and *hypoglyc** to account for alternate spellings). When possible, adjacency operators were used (i.e., *(sugar or glucose) adj3 blood*). We

applied a limit to humans. The EMBASE search was a derivative of the primary MEDLINE strategy.

Because the strength of causal conclusions differs among the various types of experimental and observational studies reported in the literature, this report will first provide an overview of several relevant study designs and their ability to support causal relationships. Following the overview defining the relevant study designs, we provide a guide to assist the reader in assessing the level of evidence provided by the different types of study designs summarized and described in this quarterly research review.

Research Study Designs and Evidence to Support Causal Relationships

The following section about study designs and causal relationships summarizes a comprehensive discussion of these topics by Elwood¹. The simplest, most direct test of causation in health is an experimental study in which we have two groups of people who are as similar as possible in all of their relevant characteristics, and we then apply the suspected (i.e. putative) causal factor to one group. Relevant characteristics are those factors, other than the one being studied, which could affect the frequency or severity of occurrence of the disease or condition. In studies of human health, this type of experiment is called a **randomized controlled trial (RCT)**. In appropriate circumstances, RCTs are considered the “gold standard” or best possible method for deriving causal evidence.

However, for practical and ethical reasons, RCTs are not always appropriate. RCTs can only be used to assess methods of treatment that are likely to be beneficial. In studies of human health, many important relationships are those in which we are concerned about harmful, rather than beneficial, effects or exposures. This is the case in conducting studies to establish whether diabetes has an adverse effect on periodontal health. On the other hand, RCTs involving periodontal treatment are appropriate in providing evidence to demonstrate that treating periodontal infection contributes to improved glycemic control or perhaps reduces the risk of development of diabetes or its complications. However, in studying the role of periodontal disease in the pathogenesis of diabetes or its complications, the RCT might be impractical because of the length of time required to observe complications or to diagnose diabetes or the large number of participants required to demonstrate such a causal relationship.

Analytical Observational Study Designs: Cohort, Case-control, and Cross-sectional Studies

Because of the ethical, methodological, and practical limitations of experimental studies (RCTs) for answering questions about causation for many types of health-related issues, other study designs are

also used. The three main types of analytical, non-experimental study designs used to support or explore causal relationships in human health are the cohort, case-control, and analytical cross-sectional study designs. These three study designs are considered “observational” studies because no intervention is used. They differ in the way study participants are chosen and the relationship in time between the occurrence of exposure to the putative causal factor and the occurrence of the disease or condition, which we will refer to as the “outcome”.

Cohort studies compare groups of people exposed to a putative causal factor with those who are not exposed. The exposures are identified at a point in time when none of the people in either group have the outcome of interest. The groups are observed over a period of time to compare differences between the groups in the occurrence of the outcome.

Case-control studies compare a group of people who have already experienced the outcome (cases) with a group of similar people without the outcome (controls). Investigators then look backward in time, or retrospectively, to assess the frequency with which the cases and controls were exposed to the putative causal factor in the time period prior to the diagnosis of the outcome.

Cross-sectional studies select participants who comprise a population or are considered a sample of people representative of a population. All data on the putative causal factor (or exposure) and the outcome are collected at the same point in time, i.e. a cross-section in time. One is able to assess whether there is an association between the putative causal factor and the outcome by comparing differences in the frequency of the outcome in those who have the putative causal factor with people who do not. Although a greater frequency of the outcome may be observed in the people exposed to the putative causal factor, we are limited in our ability to make causal inferences about the relationship because the time sequence of events cannot be established.

The variation in the strength of evidence due to different study designs has led to the development of several schemes providing a hierarchy of evidence to rank studies according to the way in which their design contributes to the strength of evidence provided. The hierarchy is a way to reflect the potential of each type of study design to answer a particular type of question, based on the probability that its design has minimized the impact of bias on the results². The hierarchy in the following table is an ordering of the strength of the evidence each properly designed study type can yield².

Evidence hierarchy adapted from the Australian Government’s National Health and Medical Research Council’s designation of ‘levels of evidence’ according to type of research question (see also explanatory notes below this table)².

Level	Intervention ¹	Etiology ²
I ³	A systematic review of level II studies	A systematic review of level II studies
II	A randomised controlled trial	A prospective cohort study
III-1	A pseudorandomised controlled trial (i.e. alternate allocation or some other method)	All or none ⁴
III-2	A comparative study with concurrent controls: <ul style="list-style-type: none"> ▪ Non-randomized, experimental trial⁵ ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group 	A retrospective cohort study
III-3	A comparative study without concurrent controls: <ul style="list-style-type: none"> ▪ Historical control study ▪ Two or more single arm study⁶ ▪ Interrupted time series without a parallel control group 	A case-control study
IV	Case series with either post-test or pre-test/post-test outcomes	A cross-sectional study or case series

Explanatory notes

¹ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b).

² If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the ‘Intervention’ hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (ie. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the ‘Aetiology’ hierarchy of evidence should be utilized.

³ A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result, as different studies (and study designs) might contribute to each different outcome.

⁴ All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

⁵ This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (ie. utilize A vs B and B vs C, to determine A vs C with statistical adjustment for B).

⁶ Comparing single arm studies ie. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs B and B vs C, to determine A vs C but where there is no statistical adjustment for B).

1. Adverse Effects of Diabetes on Periodontal Health: Evidence from Observational Studies

To address the question of whether diabetes adversely affects periodontal health, it is not ethical to use an RCT in humans, because that would require the researchers to cause some individuals to develop diabetes. Therefore, the evidence about whether or not diabetes adversely affects periodontal health must come from observational studies.

The evidence that diabetes adversely affects periodontal health comes from studies conducted in each of the world's continents. The variety in the body of evidence comes not only from the geographic origins of the reports. The variety also is determined by the study designs and methods of conducting the investigations. These factors help determine the kinds of conclusions about causality that can be inferred from the results. Causality, or causation, relevant to factors in human health issues can be defined as follows: A factor is a cause of a disease or health-related condition if its operation increases the frequency of the disease or condition¹.

As might be expected, reports in the literature provide answers to different kinds of questions and vary in their ability to help us understand how diabetes can be considered a cause of poorer periodontal health. They also vary in our ability to establish how strong that relationship is. The majority of the reports are cross-sectional studies that provide information about the association between diabetes and the prevalence of periodontal diseases. Cross-sectional studies provide information on the prevalence, extent, and severity of periodontal disease in people with diabetes at a single point in time. Because all measurements are performed at a single point in time, we are limited in our ability to make conclusions about causality from cross-sectional studies. However, the cross-sectional study design does allow comparing the differences in percents or proportions of individuals with periodontal disease between those with and without diabetes. Cross sectional studies also allow testing hypotheses about how strongly associated a suspected causal factor may be with an outcome and if there is a dose response (e.g. how much more likely are people with poorer glycemic control to have more severe periodontal disease than those with better glycemic control?). The vast majority of cross-sectional studies reporting on prevalence of periodontal disease conclude the prevalence of periodontal disease is greater in people who have diabetes. Table 1 displays an up-to-date summary of the conclusions of all such studies currently accessible and will be described in greater detail in a subsequent section. The studies presented in Table 1 are described collectively in several comprehensive reviews³⁻⁸.

The strongest type of evidence supporting the role of diabetes contributing to poorer periodontal health comes from cohort studies evaluating the incidence (the rate of new cases of periodontal disease over time) and progression (a measure of the worsening of periodontal status over time) of periodontal disease. Cohort studies must follow people *over time* and hence can allow for conclusions to contribute to establishing a causal relationship between diabetes and poorer periodontal health. These studies also allow quantification of the degree to which diabetes increases the risk for periodontal disease incidence, severity, or progression. All of the cohort study reports shown in Table 1 and eight of the ten cohort study reports shown in Table 2 support diabetes mellitus and degree of glycemic control, respectively, associated with greater risk for incidence, severity, or progression of periodontal disease.

Table 1 summarizes the conclusions of studies reported in the literature that address the question of whether diabetes adversely affects periodontal health. To interpret the contents of Table 1, first look at the column headings and then the row headings. The column headings indicate the type of diabetes included in the study and the row headings indicate the type of study. Notice that there are both cohort and cross-sectional studies that have addressed the question of whether diabetes has an adverse effect on periodontal health. It is important to keep in mind that RCTs would not be appropriate for addressing the question summarized in Table 1, i.e. whether diabetes adversely affects periodontal health, because it would be unethical to use an intervention in humans that caused diabetes in an experimental group. Therefore, the highest level of evidence useful in addressing this question would come from the results of cohort studies.

In each category (group of studies) within Table 1, the numerator is the number of studies confirming that diabetes adversely affects one or more of several measures of periodontal health (e.g. gingivitis, probing pocket depth, attachment loss, or radiographic bone loss). The denominator represents the total number of studies of that particular kind (e.g. cross-sectional studies with participants having type 2 diabetes). For example, all four out of the four reports from cohort studies that included people with type 2 diabetes concluded that periodontal health was worse in people who had diabetes than in those without diabetes. Similarly, all three of the reports investigating gestational diabetes mellitus (GDM) concluded that women with GDM were more likely to have poorer periodontal health than pregnant women without GDM. The bottom row shows there are roughly equal numbers of studies of reporting on type 1 diabetes (27) and type 2 diabetes (29), exclusively. Also, only three reports address GDM, so far. From the information presented in Table

1 we can see the vast majority of reports, namely 83 of 94 studies as shown in the extreme bottom right corner, provide evidence that diabetes adversely affects periodontal health.

Another set of studies in the literature addresses the question of whether the *degree* of glycemic control of diabetes is associated with poorer periodontal health. The degree to which diabetes is controlled or managed is usually assessed by measuring the amount of hemoglobin A1c (HbA1c) in the blood. This is also called glycosylated (or glycated) hemoglobin. HbA1c is a measure of how much glucose has been present in the blood and has attached to the hemoglobin in the red blood cells over the lifetime of those cells. Blood from a simple finger stick can be analyzed, and the result indicates the level of control of glycemia for the previous 60 to 90 days, reported as a percent. The current therapeutic target for HbA1c is a level less than 7%. People without diabetes usually have a level of 4.5% - 6%.

Table 2 summarizes the conclusions of studies that provided information comparing the effects of better or poorer glycemic control on periodontal health in people with diabetes. Similarly to Table 1, the evidence comes from both cohort and cross-sectional studies, as indicated in the row titles of the table; the column headings indicate the type of diabetes of the participants in the studies. The majority of the studies in Table 2 concluded that people with poorer glycemic control had worse periodontal health than those with better glycemic control (43 of the 62 studies). The stronger evidence comes from the set of cohort studies that followed people over time, allowing for more definitive conclusions regarding causality. Eight of the ten cohort study reports supported the conclusion that poorer glycemic control lead to poorer periodontal health over time.

Although the vast majority of the studies summarized in Tables 1 and 2 are cross-sectional and involve convenience samples of patients, principally from hospitals and clinics, the smaller sub-set of cohort and population-based studies support the association between diabetes and poorer periodontal health. Studies comprising this body of evidence were conducted in different settings and different countries, with different ethnic populations and age mixes, and with a variety of measures of periodontal disease status (i.e. gingival inflammation, pathologic probing pocket depth, loss of periodontal attachment, or radiographic evidence of alveolar bone loss). The studies employed different parameters to assess periodontal disease occurrence (prevalence, incidence, extent, severity, or progression). Hence this inevitable variation in methodology and study

populations limits the possibility that the same biases or confounding factors were operational in all the studies and provides support for concluding that diabetes is a risk factor for periodontal disease incidence, progression, and severity. In addition, there is substantial evidence to support a “dose-response” relationship, i.e. as glycemic control worsens, the adverse effects of diabetes on periodontal health become greater. Finally, there are no studies in the world-wide body of evidence with superior design features to refute this conclusion.

The findings and conclusions from this narrative review are consistent with three published meta-analyses that have provided additional information assessing the quality of the individual studies and quantitative summaries of the adverse effects of diabetes on periodontal health (*Papapanou, 1996*; *Khader et al., 2006*; and *Chavarry et. al., 2009*). Additionally, examples of other comprehensive narrative reviews with further details describing the studies in this body of literature are presented in articles by Khader ³, Mealey and Ocampo⁵, Mealey and Rose⁶, Lamster et al. ⁴, Taylor and Borgnakke ⁷⁻⁹, and Chavarry et. al. ⁴⁰

2. Adverse Effects of Periodontal Infection on Glycemic Control in Diabetes:

The question addressed in this next section is whether periodontal infection adversely affects glycemic control in people with diabetes. There is a growing body of evidence supporting the long-held clinical observation that periodontal infection adversely affects glycemic control.

2a. Empirical Evidence from Non-Surgical Periodontal Treatment Studies

More direct, empirical evidence regarding the effects of periodontal infection on glycemic control of diabetes comes from treatment studies using non-surgical periodontal therapy and observational studies. The treatment studies are a heterogeneous set of 35 reports that include eleven randomized clinical trials (RCTs) and 24 non-randomized clinical treatment studies as displayed in [Table 3](#). The RCTs used control groups that were either non-treated controls, positive controls (i.e. the control group received a relatively less intense form of periodontal treatment), or controls advised to continue their usual dental care. Of the eleven RCTs reviewed, seven reported a beneficial effect of periodontal therapy.

Among the set of 24 periodontal treatment studies that were not RCTs, 13 reported a beneficial effect on glycemic control and eleven did not. It is remarkable that only two of these 24 studies included control or comparison groups. Like the RCTs, there was marked variation in the use of adjunctive antibiotics, with five of the seven studies that used systemic antibiotics reporting a beneficial effect on glycemic control and one finding a numerical decrease in the HbA1c level that did not reach statistical significance.

For the body of literature consisting of both RCTs and non-RCTs, there is marked heterogeneity in the studies' designs, geographic locations, source populations, conduct, length of follow-up for glycemic control assessment, types of participants and their baseline periodontal disease and glycemic control status, inclusion of control groups, periodontal treatment protocols, sample size and power to detect differences in periodontal and metabolic response, and specific hypotheses tested¹⁰. In short, there is no group of RCTs, sufficiently similar, to unequivocally establish the effect of periodontal therapy on glycemic control. The details of the variation in this body of literature have been extensively described in several reviews¹¹⁻¹³. The review by Darré et al., published in 2008, is the most current systematic review and meta-analysis on the effect of periodontal therapy on glycemic control. This systematic review identified 25 interventional studies providing numerical information on HbA1c; 16 were non-controlled trials and nine were controlled studies. The meta-analysis, based on the combined data from the nine controlled studies suggested that periodontal treatment could lead to a significant (0.79%) reduction in HbA1c values. Darré and colleagues cautioned that a single randomized controlled trial with sufficient statistical power would be important to confirm their meta-analysis results. This caution was based principally on two factors. One was the lack of robustness of their meta-analysis results after a sensitivity analysis revealed that deletion of one particular study from analysis led to a marked diminution in the effect of periodontal therapy to a non-significant 0.27% reduction of HbA1c. The second caution was consideration of the deficiencies in the design of some of the included studies, as revealed by the report's quality analysis. The methodological ranking, or judged quality, of the nine interventional studies ranged from 85% to 30%, with 100% being the highest possible quality score.

Table 4 provides additional information about the eleven RCTs summarized in Table 3. For each study, information on the number of participants and the type of diabetes included is given, along with indication of whether antibiotics were used in conjunction with the treatment. The type of any antibiotics used and information on their dispensing mode (local, systemic, rinse) can be seen in the

table's footnote marked with one asterisk (*). Finally, in the column furthest right is the outcome achieved, indicating whether the study treatment resulted in improved glycemic control as measured by a decrease in the level of glycosylated hemoglobin (HbA1c).

One remarkable observation regarding Table 4 is the relatively small numbers of participants in each of the studies. This is mostly due to the immense resources required for conducting clinical trials, especially those that have a long follow-up period. Also, it is difficult to identify individuals meeting inclusion criteria and free of exclusion criteria and to recruit, enroll, and keep participants returning for all study visits that typically are of long duration due to their many components (e.g. interview, clinical examination, blood draw, radiographic exposure, and initial therapy and maintenance visits) in such clinical studies that last several months or years.

An important source of variation in the RCTs is the use of adjunctive antibiotics with the non-surgical periodontal therapy. Among the seven RCTs that included adjunctive antibiotics, five used the antibiotics systemically^{12, 14-17} and two locally delivered^{18, 19}. Six of these seven RCTs using antibiotics showed beneficial effects on glycemic control^{12, 15-19}. However, it is important to note the greatest improvement for one study was in the positive control group that did *not* receive the systemic antibiotic¹⁶. Also, one of the six RCTs reporting a beneficial effect did not use any antibiotics²⁰. Hence, to date there is no clear-cut evidence to support a requirement for the use of antibiotics in combination with non-surgical periodontal treatment in order to observe an improvement in glycemic control associated with non-surgical periodontal therapy. The use of adjunctive (local or systemic) antibiotics remains controversial, so additional, well-conducted studies would help to evaluate adjunctive antibiotic effectiveness in terms of type, route of administration, dose, and indication based on level of glycemic control¹¹.

2b. Periodontal Infection Adversely Affecting Glycemic Control: Empirical Evidence from Observational Studies

Additional evidence to support the effect of periodontitis on increased risk for poorer glycemic control comes from a small number of observational studies. A longitudinal epidemiological study of the Pima Indians in Arizona, USA, found subjects with type 2 diabetes in good to moderate control and with severe periodontitis at baseline were approximately six times more likely to have poor glycemic control at approximately 2-years follow-up than those without severe periodontitis at baseline²¹. In another observational study of 25 adults aged 58 to 77 years with type 2 diabetes, Collin et al. also reported a significant association between advanced periodontal disease and

impaired metabolic control²². There are no additional, more current observational longitudinal (or cohort) reports investigating the effect of periodontal infection on risk for poorer glycemic control

Finally, two cross-sectional studies report findings consistent with poorer periodontal health associated with poorer glycemic control. One of these studies included 127 pregnant women with diabetes and reported those with periodontitis were three and a half times more likely to have poorer glycemic control, after controlling for presence of a urinary tract infection and/or cervico-vaginal infection and a measure of compliance to recommended medical treatment for the diabetes²³. The other study analyzing the association between number of bleeding sites and degree of glycemic control (HbA1c) in six to thirteen year old children reported a statistically significant association, i.e. the HbA1c values increased (poorer control with higher HbA1c) as the number of bleeding sites increased. However, the authors determined this result would have no clinical significance²⁴ because the measure of association between number of bleeding sites and glycemic control was very small. The associations identified in these two cross sectional studies suggest potentially important hypotheses that could be explored further with observational cohort or intervention studies to explore causal relationships between poorer periodontal health and glycemic control in these two specific population groups.

3. Periodontal Infection as a Potential Risk Factor for Diabetes Complications: Empirical Evidence from Observational Studies

There is also emerging evidence that periodontal infection contributes to greater risk for diabetes complications. Diabetes complications are the conditions or diseases that people with diabetes often develop due to their diabetic status, such as increased risk of coronary heart disease, stroke, heart attack, and other cardiovascular events; nephropathy (diseases of the kidney, ultimately leading to End-Stage Renal Disease (ESRD) that requires renal dialysis for the patient to survive); neuropathy (diseases of the peripheral and autonomic nerves); retinopathy (diseases of the retina in the eye, possibly leading to blindness); extremely decreased wound healing; and amputations due to one or more of the complications mentioned.

It is well recognized that poor glycemic control is a major determinant for the development of the chronic complications of diabetes. Results from the landmark Diabetes Control and Complications Trial (type 1 diabetes) and the UK Prospective Diabetes Study (type 2 diabetes) demonstrated that attaining and maintaining good glycemic control could reduce the risk for and slow the progression

of microvascular complications in patients with type 1 and type 2 diabetes²⁵⁻²⁷. Additionally, the UKPDS observed a 16% reduction (P=0.052) in the risk of combined fatal or nonfatal myocardial infarction and sudden death. Further epidemiological analysis from the UKPDS showed a continuous association between the risk of cardiovascular complications and glycemia; every percentage point decrease in HbA1c (e.g. 9% to 8%), was associated with 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality, and 18% reduction in combined fatal and nonfatal myocardial infarction²⁸.

Three observational studies have provided evidence regarding the association between periodontal disease and the risk for diabetes complications. Thorstensson and colleagues²⁹ studied 39 case-control pairs of individuals with type 1 and type 2 diabetes for six years median follow-up time in Jönköping, Sweden. In each pair, the cases had severe alveolar bone loss and controls had gingivitis or minor alveolar bone loss. They found that cases were significantly more likely to have prevalent proteinuria, and cardiovascular complications including stroke, transient ischemic attacks, angina, myocardial infarction, and intermittent claudication than controls at their follow-up medical assessments.

Two reports from the on-going longitudinal study of diabetes and its complications in the Gila River Indian Community in Arizona, USA, conducted by the National Institute of Diabetes and Digestive and Kidney Diseases, address nephropathy and cardiovascular disease. Saremi and colleagues³⁰ studied a cohort of 628 individuals for a median follow-up time of 11 years. Individuals with severe periodontal disease had 3.2 times greater risk for cardio-renal mortality (i.e. ischemic heart disease and diabetic nephropathy combined) than those with no, mild, or moderate periodontal disease. This estimate of significantly greater risk persisted while controlling for several major risk factors of cardio-renal mortality including: age, sex, diabetes duration, HbA1c, body mass index (BMI), hypertension, blood glucose, cholesterol, electrocardiographic abnormalities, macroalbuminuria, and smoking.

In the second report, Shultis and colleagues³¹ investigated the effect of periodontitis on risk for development overt nephropathy (macroalbuminuria) and end-stage renal disease (ESRD) in a group of 529 Gila River Indian Community adults with type 2 diabetes. Their proportional hazards models analyses, adjusted for age, sex, diabetes duration, body mass index, and smoking, indicated periodontitis and edentulism were significantly associated with the risk of developing overt nephropathy and ESRD. The incidence of macroalbuminuria was 2.0, 2.1, and 2.6 times greater in

individuals with moderate or severe periodontitis or in those who were edentulous, respectively, than those with none/mild periodontitis. The incidence of ESRD was also 2.3, 3.5, and 4.9 times greater for individuals with moderate or severe periodontitis or for those who were edentulous, respectively, than those with none/mild periodontitis.

Since the report by Shultis and colleagues there been no new reports published on increased risk for complications of diabetes associated with periodontal infection.

4. Periodontal Infection as a Potential Risk Factor for Development of Diabetes: Empirical Evidence from Observational Studies

In addition to evidence supporting periodontal disease as a potential risk factor for developing diabetes complications, there is also evidence emerging that periodontal disease may be a risk factor for the development of type 2 diabetes and possibly gestational diabetes. Demmer and colleagues³² investigated the association between periodontal disease and the development (i.e. incidence) of new diabetes cases in a representative sample of the U.S. population, analyzing data from the first National Health and Nutrition Examination Survey (NHANES I) and its Epidemiologic Follow-up Study (NHEFS). The average follow-up period for the 9,296 individuals in the analysis was 17 years, for the time period 1971 to 1992. The study was a cohort study design because the information on the exposure (i.e. the hypothesized causal factor), the presence or absence of periodontal disease, was known at the time the study began, and the outcome (development of diabetes) was assessed subsequently. This study concluded having periodontal disease was significantly associated with a 50-100% greater risk for developing type 2 diabetes, after controlling for other established risk factors for diabetes. The greater risk for diabetes was also consistent with previous research using NHANES I and NHEFS in which risk factors for diabetes that did not include periodontal disease, for example, measures of adiposity (body mass index and subscapular skinfold thickness), having hypertension, and increased age, were also statistically significant³³. The Demmer et al. paper is an important study because it is U.S. population-based and is the first report providing evidence to support considering periodontal disease as a risk factor for the occurrence of diabetes. While this study's longitudinal design provides evidence for a causal relationship, as the single cohort study addressing this question, it is premature to consider this relationship firmly established.

Dasanayake and colleagues³⁴ investigated, in a case-control study, whether or not pregnant women who develop gestational diabetes, compared to pregnant women who do not develop gestational diabetes, had poorer clinical periodontal health and/or demonstrated higher levels of other biological markers of periodontal disease approximately two months before their gestational diabetes diagnosis. The other biological markers included bacteriological (in dental plaque and cervico-vaginal samples), immunological, and periodontitis-related inflammatory mediator analytes. This study found women who had higher levels of *Tannerella forsythia*, a recognized periodontal pathogen, in the vaginal flora were statistically significantly more likely to develop gestational diabetes than those women with lower levels. The Dasanayake et al. study concluded that *Tannerella forsythia* in the vaginal flora is a potential risk factor for gestational diabetes. Previous cross-sectional published reports^{35,36} have described an association between gestational diabetes and poorer periodontal health. The case-control study by Dasanayake et al. reports on a possible role for periodontal infection on the occurrence of gestational diabetes. This report provides a potentially important result that will most likely stimulate interest in further follow up investigations.

Summary and Conclusions

The evidence reviewed in this report supports the conclusion that a bi-directional association exists between diabetes mellitus and periodontal health; diabetes is associated with increased development and progression of periodontitis, and, while not yet firmly established, the evidence suggest periodontal infection is associated with poorer glycemic control in people with diabetes.

There is also evidence emerging that gestational diabetes may adversely affect periodontal health. Additionally, evidence is emerging to suggest that periodontal disease is associated with increased risk for diabetes complications, may be associated with the development of type 2 diabetes, and perhaps the development of gestational diabetes.

While treating periodontal infection in people with diabetes is clearly an important component in maintaining oral health, it may also play an important role in establishing and maintaining glycemic control; and possibly in delaying the onset or progression of diabetes and its complications. Therefore, dental health professionals might fulfill an important role in maintaining or improving the health, and ultimately the quality of lives, of individuals with diabetes and gestational diabetes as

well as aiding in lessening the immense burden of diabetes and periodontal diseases on our society in general.

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TABLES

Table 1. Effects of Diabetes on Periodontal Health: Conclusions of the 94 Studies that Include a Non-Diabetes Control Group.

(Note: The numerator represents the number of studies reporting diabetes having an adverse effect on periodontal health, the denominator the total number of studies in each group: # Studies with Effect/Total # Studies).

Study Design	Diabetes Mellitus Type					Total Number of Studies (#with Effect / #All Studies)
	Type 1	Type 2	Type 1 or 2	Gestational (GDM)	Type Not Reported	
Cohort (Evidence levels II and III-2)	3/3	4/4	0/0	0/0	0/0	7/7
Cross-sectional (Evidence level IV)	22/24	22/25	15/18	3/3	13/17	76/87
Total:	25/27	26/29	15/18	3/3	13/17	83/94

Table 2. Effects of Degree of Glycemic Control on Periodontal Health: Conclusions of the 62 Studies.

(Note: The numerator represents the number of studies reporting increasing degree of glycemic control having decreasing adverse effect on periodontal health, the denominator the total number of studies in each group: # Studies with Effect/Total # Studies).

Study Design	Diabetes Mellitus Type				Total Number of Studies (#with Effect / #All Studies)
	Type 1	Type 2	Type 1 or 2	Type Not Reported	
Cohort (Evidence levels II and III-2)	4/4	3/3	1/3	0/0	8/10
Cross-sectional (Evidence level IV)	11/18	15/17	7/11	2/6	35/52
Total:	15/22	18/20	8/14	2/6	43/62

Table 3. Effects of Non-surgical Periodontal Therapy on Glycemic Control:
Conclusions of the 35 Studies.

(Note: The numerator represents the number of studies reporting non-surgical therapy being associated with increasing degree of glycemic control, the denominator the total number of studies in each group: # Studies with Effect/Total # Studies).

Study Design	Number of Studies with Significant Improvement in Glycemic Control / All Studies
<u>Randomized Clinical Trials (RCTs):</u>	
Non-treated control group	2/4
Positive (i.e. less intensely treated) control group	5/6
Usual source of care control group	0/1
<i>Total RCTs:</i>	<i>7/11*</i>
<u>Non-randomized Clinical Treatment Studies (Non-RCTs):</u>	
Non-treated control group	1/2
No control group	12/22
<i>Total Non-RCT</i>	<i>13/24</i>
Total All Non-surgical Treatment Studies (RCTs + Non-RCTs):	
	20/35

* These 11 RCT studies are further described in Table 4.

Table 4. Effects of Non-surgical Periodontal Therapy on Glycemic Control (HbA1c): Descriptions and Conclusions of the Eleven Randomized Clinical Trials (RCTs) Summarized in Table 3.

Clinical Study Design by Type of Control Group	Sample Size	Diabetes Type	Adjunctive Antibiotics Used*	Statistically Significant Beneficial Effect on HbA1c
<u>RCT with Non-treated Control Group:</u>				
Aldridge et al., study 1 (1995) ³⁷	31	1	No	No
Aldridge et al., study 2 (1995) ³⁷	22	1	No	No
Kiran et al. (2005) ²⁰	44	2	No	Yes
Katagiri et al. (2009) ¹⁸	49	2	Yes ^c	Yes
<u>RCT with Positive (i.e. Less Intensely Treated) Control Group:</u>				
Grossi et al. (1997) ³⁸	113	2	Yes ^a	Yes
Al-Mubarak et al. (2002) ³⁹	78	1, 2	No	No
Rodrigues et al. (2003) ¹⁶	30	2	Yes ^b	Yes ^{**}
Skaleric et al. (2004) ¹⁹	20	1	Yes ^c	Yes
Yun et al. (2007) ¹⁷	46	2	Yes ^a	Yes
O'Connell et al. (2008) ¹⁵	30	2	Yes ^a	Yes
<u>RCT with Usual Source of Care Control Group:</u>				
Jones et al. (2007) ¹⁴	165	2	Yes ^a	No

*Adjunctive Antibiotics Type: a): Systemic doxycycline; b) Amoxicillin and augmentin; c) Minocycline, locally delivered.

**The group *not* receiving antibiotic showed greater improvement.