DOI: 10.1111/prd.12271

REVIEW ARTICLE

WILEY Periodontology 2000

Effects of periodontal disease on glycemic control, complications, and incidence of diabetes mellitus

Robert J. Genco[1] | Filippo Graziani[2] | Hatice Hasturk[3]

[1]Departments of Oral Biology, and Microbiology and Immunology, Center for Microbiome Research, University at Buffalo, Buffalo, New York, USA

[2]Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy

[3]The Forsyth Institute, Cambridge, Massachusetts, USA

Correspondence
Robert J. Genco, Departments of Oral Biology, and Microbiology and Immunology, Center for Microbiome Research, University at Buffalo, Buffalo, NY, USA.
Email: rjgenco@buffalo.edu

1 | INTRODUCTION

Diabetes, especially if poorly controlled, can increase the risk of periodontal disease and ultimately tooth loss. On the other hand, in individuals with diabetes, concurrent periodontitis can adversely affect glycemic control and increase the risk of complications such as cardiovascular disease, retinopathy, and kidney disease. This has been called the "2-way street", describing the bidirectional link between diabetes and periodontal disease. In this review, we will focus on the effects of periodontal disease on glycemic control and complications of patients with diabetes. We will also review the emerging evidence of the effects of periodontitis on increasing the risk of incident diabetes and prediabetes. Diabetes is a major cause of death and morbidity and is increasing in prevalence. Periodontal disease is one of the most common chronic infections of man, hence the reciprocal adverse relationship between these diseases is of great importance in clinical practice and in design of public health measures to manage these diseases.

2 | THE BURDEN OF DIABETES

Diabetes mellitus is a group of metabolic disorders in which hyperglycemia occurs, resulting from definitive insulin function and/or reduced insulin production. In the USA, 30.3 million individuals (9.4% of the population) had diabetes in 2015. The prevalence increases with age, and 1 in 4 adults aged ≥65 years affected by diabetes. About 25% of those with diabetes in the USA are unaware of having the disease. Type 2 diabetes accounts for ~90% of the cases in the USA, whereas type 1 diabetes, caused by autoimmune beta cell destruction, and gestational diabetes mellitus, accounts for the majority of the remaining cases.[1] There are other types of diabetes that are caused by a genetic defect in insulin secretion or insulin production (monogenic diabetes, congenital diabetes), diseases (cystic fibrosis-related diabetes), or drugs/chemicals (steroid diabetes), which can be misdiagnosed as type 1 or type 2 diabetes.

One 3rd of adults in the USA have prediabetes with elevated levels of blood glucose which predisposes to diabetes, with almost a half of adults aged >65 years being affected.[2] Hyperglycemia affects 16% or 1-in-6 pregnancies worldwide, of which 84% are a result of gestational diabetes.[3] A large proportion of women with gestational diabetes mellitus will eventually develop type 2 diabetes. For example, they are 17 times more likely to do so in the 3-6 years postpartum than women without gestational diabetes mellitus.[4] The estimated number of adults with type 2 diabetes globally almost tripled between 2002 and 2017, not only reflecting increases in the USA, but also in most other countries in the last 2 decades.[2]

3 | DIABETES COMPLICATIONS

Complications of diabetes include acute and chronic complications such as dehydration, poor wound healing, myocardial infarction, stroke, limb ischemia, kidney disease, neuropathy, neurocognitive decline, hyperosmolar coma, retinopathy, and serious foot infections.[5]

People with diabetes and chronically poor glycemic control experience death, heart disease, and stroke at rates that are 2-4 times higher than those without diabetes.[6,7] Diabetic retinopathy is the leading cause of new cases of blindness, and diabetic kidney disease is the leading cause of kidney failure in the USA.[5] As the incidence of diabetes increases, so do the complications leading to significant morbidity and mortality. Since it is mainly hyperglycemia (especially of long duration) that leads to complications, they are similar for most types of diabetes.

4 | BURDEN OF PERIODONTAL DISEASE

There is recent evidence of a significantly greater burden of periodontitis among US adults than reported previously.[8] An accurate estimate of prevalence of periodontitis using whole mouth probing among US adults aged ≥30 years comes from the National Health and Nutrition Examination Survey (NHANES) cycles 2009-2012.[9] Using the Chronic Disease Control and Prevention/American Academy of Periodontology definition of mild, moderate, and severe periodontitis, this study found that the prevalence of total periodontitis is 46.5%.[10] Importantly, in US adults aged ≥65 years, almost 2 of 3 (62.3%) among those with diabetes had periodontitis,[9] meaning that 18 900 000 individuals (5.4% of the US adult population) have both diabetes and periodontitis. This high burden of periodontal disease is observed globally.[11] Severe periodontal disease is the sixth most prevalent disease in the world.[12] Globally, higher levels of periodontal disease are seen in populations with poorly controlled diabetes, as well as those with HIV.[9,12]

5 | EFFECT OF PERIODONTITIS ON GLYCEMIC CONTROL, AND COMPLICATIONS IN INDIVIDUALS WITH DIABETES

Recent systemic reviews of studies investigating the effects of periodontal disease on glycemic control in diabetic individuals show a worsening of glycemic control over time in those with periodontitis.[13,14] There is also strong evidence that diabetic subjects with periodontitis affected by more severe diabetic complications than those with little or no periodontitis. One of the first studies showing the effect of periodontitis on glycemic control in patients with diabetes comes from a study of individuals in the Gila River Indian community. Among the native Americans in this community type 2 diabetes prevalence is very high, approaching 50%. In a longitudinal study of this population, severe periodontitis at baseline was associated with poorer glycemic control at follow-up after 2 years in those with both diabetes and periodontal disease compared with those with diabetes and little or no periodontal disease.[15]

Further studies of the Gila River Indian community found that death from cardiovascular disease and diabetic nephropathy increased in those individuals with diabetes and periodontitis compared with those with diabetes and little or no periodontitis.[16] Periodontitis was a predictor for future ischemic heart disease and diabetic nephropathy after adjusting for age, sex, diabetes duration, glycated hemoglobin, macroeconomic study, body mass index, cholesterol, hypertension, electrocardiogram abnormalities, and smoking in this study. The systematic analyses of Borgnakke et al. and Graziani et al.[13,14] summarized studies that confirm and extend these findings showing that retinopathy, diabetic nephropathy, neuropathic foot ulceration, proteinuria, cardiovascular complications, and death are correlated with the severity of periodontitis in individuals with diabetes.

A wide array of diabetic complications has been particularly associated with deterioration of periodontal status. These associations have been noticed for both type 1 and type 2 diabetes. Retinopathy has been largely associated with deterioration or progression of periodontitis in a dose-dependent manner.[16-19] Cardiovascular complications, including cardiovascular mortality, coronary heart disease or cerebrovascular events, and subclinical heart disease, have been significantly associated with type 2 diabetes.[20-22] Subjects with diabetes and periodontitis show a higher mortality rate, both for cardiovascular death and for all-cause mortality, over a 10 year period compared with subjects with diabetes alone.[23]

Implications for clinical practice and public health arising from these studies include:

- Clinicians should be aware of the "2-way street" or disease cycle that results in greater periodontal disease in those with diabetes and poorer glycemic control in those with diabetes and periodontitis. In their clinical practice, healthcare providers should inform patients with diabetes of this link and engage in oral health education programs. Patients should be aware that proper periodontal treatment may have beneficial effects on their glycemic control and diabetes complications. Patients should be advised that the cycle linking periodontal disease and diabetes can be managed for better oral and general health.
- Diabetologists and physicians should seek evidence for the presence of periodontitis in patients with diabetes, and ask about signs and symptoms (bleeding gums, drifting dentition, tooth mobility, halitosis, and gum soreness), and in case of a positive history, a referral to an oral health practitioner should be encouraged.
- Oral care providers should perform a periodontal examination in each newly diagnosed case of diabetes and an annual periodontal evaluation should be recommended for all patients of any age with diabetes. Periodontitis should be treated with no delay and oral rehabilitation should be suggested in order to restore masticatory function.

6 | EFFECTS OF PERIODONTITIS ON THE INCIDENCE OF NEW CASES OF DIABETES

An emerging series of studies has suggested that periodontitis may play a role in the incidence of new cases of type 2 diabetes, and possibly gestational diabetes.[11,13,14] In addition, there are studies that show healthy subjects with periodontitis manifest moderate hyperglycemia compared with those with little or no periodontitis. These effects of periodontitis on incident diabetes and glycemic control in healthy individuals need further study to determine the extent to which this occurs, and to provide information on the mechanisms involved. Also, further studies showing the effects of prevention and

treatment of periodontitis on metabolic control, and diabetic complications, as well as effects on hyperglycemia in healthy individuals, are needed to establish the basis for managing periodontal disease in both the management and possible prevention of diabetes.

7 | PRESENT STATUS OF STUDIES ON THE EFFECTS OF PERIODONTAL TREATMENT ON GLYCEMIC CONTROL IN PATIENTS WITH DIABETES

One of the first randomized controlled studies of periodontal treatment in individuals with diabetes was carried out on individuals from the Gila River Indian community.[24] In this study, individuals with severe periodontitis and poorly controlled type 2 diabetes were randomized to receive 5 different methods of periodontal therapy, including systemic minocycline and topical antimicrobial agents. All subjects received a complete scaling and root planing under local anesthesia, and extraction of hopeless teeth. Glycated hemoglobin levels were decreased in the groups receiving systemic antibiotics and topical chlorhexidine in addition to extraction and scaling and root planing treatment, in contrast to those only receiving extensive scaling and root planing.

This finding was of considerable interest because it suggested that effective periodontal therapy in patients with poorly controlled diabetes could reduce hyperglycemia, the hallmark pathogenic measure of diabetes. Subsequently, many studies replicated and extended these findings, although a few studies reported little or no effect of periodontal therapy on glycated hemoglobin levels. These included studies of type 1 as well as type 2 diabetes; some compared adjunctive topical as well as systemic antibiotics, and they were carried out in countries worldwide. There are 2 Cochrane systematic reviews of these studies[25,26], as well as a meta-analysis of these 2 reviews along with a critical analysis of the type 1 and type 2 diabetes studies by Madianos and Koromantzos.[27] These authors[27] assessed and rated 9 systematic reviews published during 2013-2017 as being of either high or medium quality using the multiple systematic reviews tool, which takes into account 11 criteria.[28] The average multiple systematic reviews score was 8.2 (high quality) with a range of medium (score of 7) to high quality (8-11). The studies that evaluated the reduction in glycated hemoglobin at 3-4 months after periodontal treatment showed a reduction in glycated haemoglobin, ranging from −0.27% to −1.03%. About a third of these studies reported data from 6 months after periodontal treatment, which showed a smaller degree of glycated hemoglobin reduction, ranging from −0.02% to −1.18%. There was also a reduction in fasting plasma glucose, ranging from −8.95 to −9.04 mg/dL at 3-4 months, which was consistent with the reduction in glycated hemoglobin. The results of these meta-analyses indicate that effective nonsurgical periodontal treatment in people with diabetes results in a statistically significant reduction (~0.40%; 0.27%-0.65%) in glycated hemoglobin levels at 3 months. Such a reduction in hyperglycemia, if prolonged, might reduce diabetic complications and improve quality of life.[29,30] The studies did not show any significant additional impact of adjunctive antibiotic use on glycemic control. Figure 1 shows the systematic reviews and meta-analyses evaluated in this review.

The findings of these meta-analyses are supported by a population-based US study of >5000 individuals with diabetes.[27] In this study of insurance records and dental records, patients who had periodontal surgery showed glycated hemoglobin levels 0.25% lower than in patients who had ≥1 quadrants of periodontal surgery, compared with a <0.1% reduction in those who had nonsurgical therapy.

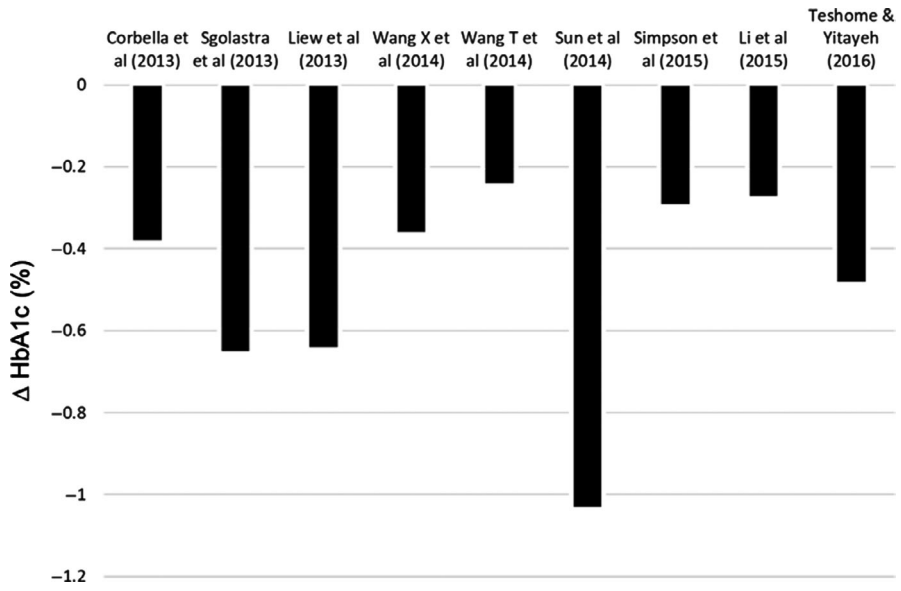

FIGURE 1 Change in glycated hemoglobin (HbA1c) at 3 mo following periodontal treatment. Nine systematic reviews and meta-analyses published during 2013-2017[26,31–38] are presented here. These reports evaluated a total of 66 individual studies, the majority of which included people with type 2 diabetes. The average glycated hemoglobin reduction was ~0.40%. Figure based on data presented in Madianos & Koromantzos[40]

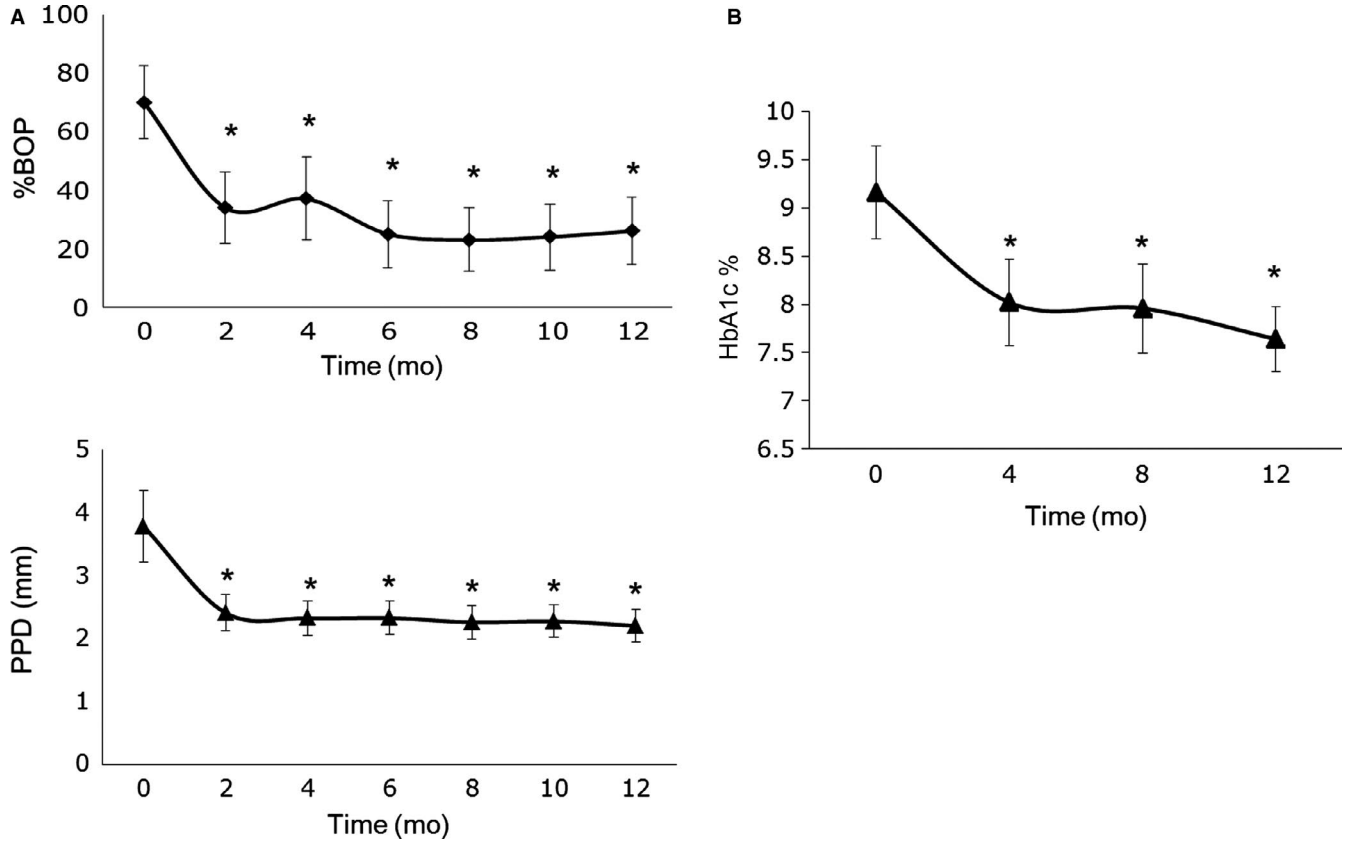

FIGURE 2 Change in glycated hemoglobin (HbA1c) following periodontal treatment. (A) Periodontal treatment directed at elimination of oral inflammation, including reduction of periodontal inflammation, periodontal pocket depth, and removal of dental disease. Following completion of active treatment phase at 2 mo mean % bleeding on probing (BOP) and periodontal pocket depth (PPD) were significantly reduced compared with baseline ($P < 0.05$ compared with baseline). During the maintenance phase, at every 2 mo recall visit, the periodontal condition maintained its level obtained at 2 mo after active treatment ($P < 0.05$ at 4, 6, 8, 10, and 12 mo visits compared with baseline). (B) Control of periodontal inflammation affected glycemic control as indicated by a statistically significant reduction in HbA1c levels following completion and maintenance of periodontal condition throughout the observation period up to 12 mo ($P < 0.05$ at 4 and 8 mo, and $P < 0.01$ at 12 mo compared with baseline). The average reduction in HbA1c was 1.3 ± 0.7% (from 9.2% at baseline to 7.6% at the end of 12 mo) without alterations in pharmacological treatment

The difference was statistically significant. Both groups had periodontitis as assessed by periodontal probing in this study. Another important population-based study of individuals with diabetes in Finland showed that those with better toothbrushing efficiency had lower plaque scores and lower glycated hemoglobin levels than those with less toothbrushing efficiency.[39] These population-based studies suggest that the effects of periodontal therapy or preventive measures in reducing glycated hemoglobin in patients with diabetes observed in highly controlled trials can be achieved in clinical practice, and through patients paying attention to good plaque control.

Reduction in glycated hemoglobin is an established outcome measure of diabetes treatment and is related to reduction in hyperglycemia as well as reduction in the risk of a number of complications of diabetes including retinopathy, kidney disease, and death.[40,41] A reduction of 0.4% in glycated hemoglobin is comparable with that achieved by adding a second antiglycemic medication to the management of hyperglycemia in a patient with diabetes, and hence is clinically significant.

A recent periodontal treatment study was conducted to evaluate the role of local inflammation in the systemic inflammatory burden and glycemic control in people with type 2 diabetes. The findings of this 12-month follow up study[42,43] following periodontal treatment are shown in Figure 2. The study included poorly controlled patients with type 2 diabetes and severe periodontal disease (n = 30). The periodontal treatment was designed to achieve a complete or near complete elimination of oral inflammation, and it consisted of a combination of nonsurgical and surgical treatment with adjunctive use of systemic and local antibiotics as well as extraction of hopeless teeth and treatment of acute dental diseases (eg, caries and endodontic lesions). After this comprehensive treatment, the patients were clinically monitored every 2 months and received repeat supportive periodontal therapy and oral maintenance as needed, as well as assessment of glycated hemoglobin levels. Paralleling the improvement in periodontal health (reduction in pocket depth and bleeding on probing, and attachment level gain), glycemic control, measured by fasting serum glucose and glycated hemoglobin, showed a steady decrease following periodontal therapy ($P < 0.05$; Figure 2). The cumulative impact of continuous and strict periodontal follow-up and maintenance at 2-month intervals following active

TABLE 1 Inflammatory cytokines and mediators in people with type 2 diabetes (T2DM; n = 16) and type 2 diabetes and periodontal disease (T2DM + chronic periodontitis; n = 24) compared with healthy individuals (n = 21)

	Healthy	T2DM	T2DM + chronic periodontitis
Granulocyte colony stimulating factor (pg/mL)	42.15 ± 5.23	48.84 ± 5.20*	50.33 ± 5.27*
Interferon-gamma (pg/mL)	5.02 ± 0.43	5.43 ± 0.44	5.15 ± 0.36
Interleukin-10 (pg/mL)	9.66 ± 0.94	7.80 ± 0.92*	4.95 ± 1.00**
Interleukin-15 (pg/mL)	6.37 ± 0.49	5.82 ± 0.51	4.10 ± 0.60**
Interleukin-4 (pg/mL)	14.15 ± 1.95	11.84 ± 1.94*	8.26 ± 2.03**
Interleukin-6 (pg/mL)	1.51 ± 0.27	2.20 ± 0.26	2.47 ± 0.32
Tumor necrosis factor-alpha (pg/mL)	6.49 ± 0.63	6.99 ± 0.63	7.08 ± 0.57
sFas ligand (pg/mL)	10.44 ± 1.82	12.52 ± 1.78	8.33 ± 1.90**
C-reactive protein (ng/mL)	21.89 ± 2.34	21.96 ± 2.38	23.41 ± 2.47**
Adiponectin	159.87 ± 15.60	159.26 ± 16.33	120.26 ± 17.83*

Results are shown as mean ± SD.
*$P < 0.05$ compared with healthy.
**$P < 0.05$ compared with T2DM.

treatment resulted in even greater (non-significant) reduction in glycated hemoglobin levels at the end of the 12-month observation period. Change in glycemic parameters in response to the periodontal treatment demonstrates that the infection and inflammation associated with periodontal disease significantly contributes to the inflammatory burden and negatively impacts the efficiency of pharmacological control of type 2 diabetes, and that reduction of this inflammation by rigorous periodontal treatment can result in better glycemic control.

8 | PATHOLOGIC MECHANISMS BY WHICH PERIODONTITIS ADVERSELY AFFECTS GLYCEMIC CONTROL AND COMPLICATIONS IN PATIENTS WITH DIABETES

Periodontal disease is a chronic inflammatory disease caused by subgingival biofilm. The inflammatory response is characterized by secretion of host-derived mediators triggered by biofilm products such as lipopolysaccharide. The major mediators include interleukin-1 beta , interleukin-6, tumor necrosis factor-alpha, and the matrix metalloproteinases, especially matrix metalloproteinases -8, -9, and -13. T-regulatory cytokines interleukin-12 and interleukin-18, and chemokines, are also involved. Bone resorption also occurs and is associated with some of the above mediators as well as prostaglandin E_2, interleukin-17, and receptor activation of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin. These mediators and inflammatory cells, as well as osteoclasts and osteoblasts, act locally, resulting in loss of the soft and hard tissues surrounding and supporting the tooth.[44]

There is evidence that these mediators are also elevated systemically in individuals with periodontitis, especially in those with both diabetes and periodontitis, leading to generalized systemic inflammation. It is proposed that this elevated systemic inflammation contributes to insulin resistance and eventually to diabetic complications. The resulting hyperglycemia can in turn activate pathways, including those involved in the formation of advanced glycation end-products, which bind to receptors, leading to increased inflammation, oxidative stress, and apoptosis.[18]

Hence, the systemic inflammatory response associated with periodontal disease may adversely affect glycemic control and complications of patients with diabetes, especially microvascular complications. This may account for the worsening of glycemic control and increased risk of complications in patients affected by both periodontitis and diabetes.

9 | INFLAMMATION COMMON TO PERIODONTAL DISEASE - DIABETES AND OBESITY

Diabetes types 1 and 2 and obesity are associated with elevated systemic inflammatory mediators.[45] These elevated levels of inflammatory mediators contribute to increasing insulin resistance, hyperglycemia, and the risk of diabetic complications including periodontal disease.

Hence, both diabetes and periodontal disease increase systemic inflammation with an increase in serum levels of mediators including interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, as well as reactive oxygen species. In addition, obesity-related systemic inflammation may contribute to both diabetes and periodontitis. For example, leptin and other obesity-related proinflammatory mediators may be important in enhancing periodontal inflammation in those affected by diabetes and obesity.[46] A study by Hasturk et al. demonstrated that individuals with type 2 diabetes and periodontal disease have increased serum levels of proinflammatory mediators such as interleukin-6, granulocyte colony stimulating factor,

tumor necrosis factor-alpha, and C-reactive protein, while also having significantly decreased levels of cytokines and mediators with anti-inflammatory actions such as interleukin-4, interleukin-15, interleukin-10, adiponectin, and soluble Fas-ligand (Table 1).

10 | WHAT IS THE MECHANISM WHICH EXPLAINS THE EFFECTS OF PERIODONTAL TREATMENT IN REDUCING HYPERGLYCEMIA (GLYCATED HEMOGLOBIN) IN PATIENTS WITH DIABETES AND PERIODONTAL DISEASE?

Periodontal treatment reduces blood levels of inflammatory mediators including tumor necrosis factor-alpha, interleukin-6, matrix metalloproteinases, and the acute phase C-reactive protein made by the liver in response to serum mediators such as tumor necrosis factor-alpha and interleukin-6.[47-51]

These are likely associated with increasing insulin resistance by interfering with the function of the insulin receptor, leading to hyperglycemia. Reducing these mediators by removing the biofilm, leading to the reduction of systemic inflammation, probably accounts for the reduction of hyperglycemia by periodontal treatment.

Differences in the subgingival microflora in patients with diabetes compared with those without diabetes may also account for the reduction of hyperglycemia with periodontal treatment. For example, 1 or more of the periodontal pathogens may produce an agent (or agents) that lead(s) directly or indirectly to insulin resistance, and therefore removal of the organism may help lower hyperglycemia. To date, studies do not show a clear difference in the subgingival microflora of periodontal disease in those with diabetes compared with healthy individuals that could account for different effects on diabetic control, although these differences may exist.[52]

Large randomized controlled intervention trials are necessary to better understand the potential for management of periodontal disease and glycemic control and related complications such as heart and kidney diseases in individuals with diabetes. These findings are important to help establish the validity of the role of periodontal disease affecting diabetes glycemic control and complications. Also, if studies are positive, then they may be important clinically, because for each reduction of 1% in glycated hemoglobin levels (like those achieved in some studies of periodontal intervention), there is an associated 25% reduction in risk for certain complications of diabetes, including death, nephropathy, and retinopathy.[29,40]

REFERENCES

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2018. *Diabetes Care*. 2018;41(Suppl 1):S13-S27.
2. International Diabetes Federation (IDF). *IDF Diabetes Atlas*, 8th ed. Brussels, Belgium: International Diabetes Federation; 2017:150. Available at: www.diabetesatlas.org. Accessed February 16, 2018.
3. Centers for Disease Control and Prevention (CDC). National diabetes statistics report, 2017; estimates of diabetes and its burden in the United States. Available at: https://www.Cdc.Gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.Pdf. Accessed December 27, 2017.
4. Song C, Lyu Y, Li C, et al. Long-term risk of diabetes in women at varying durations after gestational diabetes: a systematic review and meta-analysis with more than 2 million women. *Obes Rev*. 2018;19(3):421-429.
5. American Diabetes Association. Standards of medical care in diabetes—2018. *Diabetes Care*. 2018;41(Suppl 1):S1-S150.
6. Emerging Risk Factors C, Sarwar N, Gao P, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215-2222.
7. Singh GM, Danaei G, Farzadfar F, et al. The age-specific quantitative effects of metabolic risk factors on cardiovascular diseases and diabetes: a pooled analysis. *PLoS One*. 2013;8(7):e65174.
8. Eke PI, Thornton-Evans GO, Wei L, et al. Accuracy of NHANES periodontal examination protocols. *J Dent Res*. 2010;89(11):1208-1213.
9. Eke PI, Dye BA, Wei L, et al. Update on prevalence of periodontitis in adults in the United States: NHANES 2009 to 2012. *J Periodontol*. 2015;86(5):611-622.
10. Eke PI, Page RC, Wei L, et al. Update of the case definitions for population-based surveillance of periodontitis. *J Periodontol*. 2012;83(12):1449-1454.
11. Borgnakke WS, Ylöstalo PV, Taylor GW, et al. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *J Periodontol*. 2013;84(4 Suppl):S135-S152.
12. Kassebaum NJ, Bernabe E, Dahiya M, et al. Global burden of severe periodontitis in 1990-2010: a systematic review and meta-regression. *J Dent Res*. 2014;93(11):1045-1053.
13. Borgnakke WS, Ylostalo PV, Taylor GW, Genco RJ. Effect of periodontal disease on diabetes: systematic review of epidemiologic observational evidence. *J Clin Periodontol*. 2013;40(Suppl 14):S135-S152.
14. Graziani F, Gennai S, Solini A, et al. A systematic review and meta-analysis of epidemiologic observational evidence on the effect of periodontitis on diabetes an update of the EFP-AAP review. *J Clin Periodontol*. 2018;45(2):167-187.
15. Taylor GW, Burt BA, Becker MP, et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus. *J Periodontol*. 1996;67(suppl 10):1085-1093.
16. Noma H, Sakamoto I, Mochizuki H, et al. Relationship between periodontal disease and diabetic retinopathy. *Diabetes Care*. 2004;27(2):615.
17. Amiri AA, Maboudi A, Bahar A, et al. Relationship between Type 2 diabetic retinopathy and periodontal disease in Iranian adults. *N Am J Med Sci*. 2014;6(3):139-144.
18. Boillot A, Bouchard P, Moss K, Offenbacher S, Czernichow S. Periodontitis and retinal microcirculation in the atherosclerosis risk in communities study. *J Clin Periodontol*. 2015;42(4):342-349.
19. Song SJ, Lee S-S, Han K, Park J-B. Periodontitis is associated with diabetic retinopathy in non-obese adults. *Endocrine*. 2016;56(1):82-89.
20. Saremi A, Nelson RG, Tulloch-Reid M, et al. Periodontal disease and mortality in type 2 diabetes. *Diabetes Care*. 2005;28(1):27-32.
21. Southerland JH, Moss K, Taylor GW, et al. Periodontitis and diabetes associations with measures of atherosclerosis and CHD. *Atherosclerosis*. 2012;222(1):196-201.
22. Natto ZS, Aladmawy M, Alasqah M, Papas A. Is there a relationship between periodontal disease and causes of death? A cross sectional study. *Braz Dent J*. 2015;26(1):33-38.
23. Sharma P, Dietrich T, Ferro CJ, Cockwell P, Chapple ILC. Association between periodontitis and mortality in stages 3–5 chronic kidney

disease: NHANES III and linked mortality study. *J Clin Periodontol*. 2016;43(2):104-113.
24. Grossi SG, Genco RJ. Periodontal disease and diabetes mellitus: a two-way relationship. *Ann Periodontol*. 1998;3(1):51-61.
25. Simpson TC, Needleman I, Wild SH, et al. Treatment of periodontal disease for glycaemic control in people with diabetes. *Cochrane Database Syst Rev*. 2010;(5):CD004714.
26. Simpson TC, Weldon JC, Worthington HV, et al. Treatment of periodontal disease for glycaemic control in people with diabetes mellitus. *Cochrane Database Syst Rev*. 2015;6(11):CD004714.
27. Spangler L, Reid RJ, Inge R, et al. Cross-sectional study of periodontal care and glycosylated hemoglobin in an insured population. *Diabetes Care*. 2010;33(8):1753-1758.
28. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. *BMC Med Res Methodol*. 2007;(7):10.
29. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ*. 2000;321(7258):405-412.
30. Khaw KT, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A1c with cardiovascular disease and mortality in adults: the European prospective investigation into cancer in Norfolk. *Ann Intern Med*. 2004;141(6):413-420.
31. Corbella S, Francetti L, Taschieri S, De Siena F, Fabbro MD. Effect of periodontal treatment on glycemic control of patients with diabetes: a systematic review and meta-analysis. *J Diabetes Investig*. 2013;4(5):502-509.
32. Sgolastra F, Severino M, Pietropaoli D, Gatto R, Monaco A. Effectiveness of periodontal treatment to improve metabolic control in patients with chronic periodontitis and type 2 diabetes: a meta-analysis of randomized clinical trials. *J Periodontol*. 2013;84(7):958-973.
33. Liew AK, Punnanithinont N, Lee YC, Yang J. Effect of non-surgical periodontal treatment on HbA1c: a meta-analysis of randomized controlled trials. *Aust Dent J*. 2013;58(3):350-357.
34. Wang X, Han X, Guo X, Luo X, Wang D. The effect of periodontal treatment on hemoglobina1c levels of diabetic patients: a systematic review and meta-analysis. *PLoS ONE*. 2014;9(9):e1084412.
35. Wang T, Jen I, Chou C, Lei Y. Effects of periodontal therapy on metabolic control in patients with type 2 diabetes mellitus and periodontal disease. *Medicine*. 2014;93B(28):e292.
36. Sun QY, Feng M, Zhang MZ, et al. Effects of periodontal treatment on glycemic control in type 2 diabetic patients: a meta-analysis of randomized controlled trials. *Chin J Physiol*. 2014;57(6):305-314.
37. Li Q, Hao S, Fang J, Xie J, Kong XH, Yang JX. Effect of nonsurgical periodontal treatment on glycemic control of patients with diabetes: a meta-analysis of randomized controlled trials. *Trials*. 2015;16(1):291.
38. Teshome A, Yitayeh A. The effect of periodontal therapy on lycemic control and fasting plasma glucose level in type 2 diabetic patients: Systematic review and meta-analysis. *BMC Oral Health*. 2016;17(1):31.
39. Syrjala AM, Kneckt MC, Knuuttila ML. Dental self-efficacy as a determinant to oral health behavior, oral hygiene and HbA1c level among diabetic patients. *J Clin Periodontol*. 1999;26(9):616-621.
40. Madianos PN, Koromantzos PA. An update of the evidence on the potential impact of periodontal therapy on diabetes outcomes. *J Clin Periodontol*. 2018;45(2):188-195.
41. Chapple IL, Genco RJ. Diabetes and periodontal diseases: consensus report of the Joint EFP/AAP workshop on periodontitis and systemic diseases. *J Clin Periodontol*. 2013;40(Suppl 14):S106-S112.
42. Hasturk H, Nguyen D, Celebi F, et al. Neutrophil function and treatment response in diabetics with periodontal disease. *J Dent Res*. 2012;91(Spec Iss A):567 (www.iadr.org).
43. Hasturk H, Manosudprasit A, Stephens D, Sherzai H, Kantarci A, Van Dyke TE. Serum biomarkers in response to periodontal treatment in type 2 diabetes mellitus. *J Dent Res*. 2014;93(Spec Iss B):1425 (www.iadr.org).
44. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes*. 2005;54(6):1615-1625.
45. Dandona P, Aljada A, Bandyopadhyay A. Inflammation: the link between insulin resistance, obesity and diabetes. *Trends Immunol*. 2004;25(1):4-7.
46. Preshaw PM, Foster N, Taylor JJ. Cross-susceptibility between periodontal disease and type 2 diabetes mellitus: an immunobiological perspective. *Periodontol 2000*. 2007;45(1):138-157.
47. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. *J Clin Periodontol*. 2008;35(4):277-290.
48. D'Aiuto F, Parkar M, Andreou G, et al. Periodontitis and systemic inflammation: control of the local infection is associated with a reduction in serum inflammatory markers. *J Dent Res*. 2004;83(2):156-160.
49. Iwamoto Y, Nishimura F, Nakagawa M, et al. The effect of antimicrobial periodontal treatment on circulating tumor necrosis factor-alpha and glycated hemoglobin level in patients with type 2 diabetes. *J Periodontol*. 2001;72(6):774-778.
50. Maraccini AM, Meschiari CA, Sorgi CA, et al. Circulating interleukin-6 and high-sensitivity C-reactive protein decrease after periodontal therapy in otherwise healthy subjects. *J Periodontol*. 2009;80(4):594-602.
51. O'Connell PA, Taba M, Nomizo A, et al. Effects of periodontal therapy on glycemic control and inflammatory markers. *J Periodontol*. 2008;79(5):774-783.
52. Takahashi K, Nishimura F, Kurihara M, et al. Subgingival microflora and antibody responses against periodontal bacteria of young Japanese patients with type 1 diabetes mellitus. *J Int Acad Periodontol*. 2001;3(4):104-111.

How to cite this article: Genco RJ, Graziani F, Hasturk H. Effects of periodontal disease on glycemic control, complications, and incidence of diabetes mellitus. *Periodontol 2000*. 2020;83:59–65. https://doi.org/10.1111/prd.12271