

THE **Diabetes-Periodontal Disease Link**

– CLINICAL POINT OF VIEW

The incidence of type-2 diabetes is skyrocketing in Canada and throughout the developed world, primarily due to increasing obesity rates, sedentary lifestyles and the aging population. While six percent of the population here have been diagnosed with the disease, it has been estimated that one-third of all cases go undetected. Worldwide, more than 177 million people are afflicted with diabetes, a number that is expected to climb to 300 million by 2025.

According to Canadian Diabetes Association (CDA) Clinical Practice Guidelines, diabetes is defined as a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, insulin action or both. Diabetes is diagnosed on the basis of a fasting plasma glucose test performed in an accredited lab. A fasting plasma glucose of greater than 7 mmol/L, or a casual plasma glucose greater than 11 mmol/L, confirm the diagnosis. Normal fasting glucose is 3.5 mmol/L to 6 mmol/L; normal post-meal glucose may be as high as 7.8 mmol/L.

Frequently, a diagnosis of diabetes is made only after a person presents with one or more of its related complications, such as heart disease, kidney failure or stroke. A poorly recognized complication of diabetes is periodontal disease, which increases in severity in relation to poor glycemic control. With the growing appreciation of the link between oral and systemic health, the relationship between periodontal disease and diabetes has emerged as a key issue in diabetes care for both physician and dentist alike. Here, two leading Canadian experts discuss the issue.

Clinical POV Advisory panel:



Dr. J. Robin Conway,
Medical Director;
The Diabetes Clinic,
Smiths Falls, ON



Dr. Howard C. Tenenbaum,
Professor; Discipline in Periodontology,
Professor; Laboratory Medicine and Pathobiology
Faculty of Medicine
Director; Division of Research, Department of Dentistry
Mount Sinai Hospital
University of Toronto,
Toronto, ON

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1. What can the mouth tell us about systemic health?

DR. TENENBAUM:

It is often said that the mouth acts as a window to the body, in that under varying conditions changes to oral soft and hard tissues occur in the presence of certain systemic diseases. In fact, some systemic conditions can present first in the mouth, much earlier than other subsequent manifestations throughout the body. These include certain types of diseases that affect mucous membranes and/or skin, such as benign mucous membrane pemphigoid, pemphigus, and other somewhat less serious but nonetheless painful conditions, including erosive lichen planus. Blood malignancies such as leukemia, where leukemic infiltrates invade the gingival tissue and cause significant inflammation and gingival enlargement can also present in the mouth.

DR. CONWAY:

The tissues of the mouth can indeed act as a biologic model of how tissues elsewhere in the body are behaving. Given that the mouth is much more open to inspection than many other tissues, understanding how diseases like diabetes affect oral tissues can be an important tool for monitoring and managing patients.

Diabetes is characterized by various changes in the mouth, including increased inflammation that leads to periodontitis, and xerostomia due to the dehydration brought about through the osmotic effects of hyperglycemia. Chronic hyperglycemia also encourages oral thrush.

These inflammatory changes lead to endothelial dysfunction and atherosclerosis, leading to macrovascular complications which increase the risk of heart attack and stroke — as well as microvascular disease that can lead to kidney failure, vision deterioration and erectile dysfunction.

2. What is the relationship between diabetes and periodontal disease?

DR. CONWAY:

Diabetics are up to four times more likely to develop periodontal disease than non-diabetics. The severity of the periodontal disease increases as A1c levels rise — A1c being a measurement of glycated hemoglobin that provides an estimate of glucose levels over the preceding three months.



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Diabetics whose disease is poorly controlled seem to have the same amount of plaque as either well-controlled diabetics or non-diabetics, but the poorly controlled group responds differently to the presence of bacterial plaque at the gum line. It would be logical to postulate that this may be because higher glucose levels provide a more fertile environment for bacterial growth, thereby increasing the burden of disease-causing bacteria. But while we see a higher level of periodontal disease, we do not see a higher level of caries, and so simple bacterial growth may not provide a full explanation.

What's really at work is inflammation — poorly controlled diabetics have more harmful cytokines in their gingival tissue, causing destructive inflammation of the gums and increased periodontal bone loss. In turn, beneficial growth factors are inhibited, interfering with the healing response to infection.

It has been well established that poorly controlled diabetics tend to have elevated levels of triglycerides, which appear to be related to greater probing depths and attachment loss.

DR. TENENBAUM:

The association between diabetes and periodontal disease may be related largely to the fact that they have analogous underlying pathophysiological processes which are affected by similar genetic and epigenetic risk factors. What's fascinating about the association between diabetes and periodontal disease is their bi-directional relationship, which is well documented in both medical and dental literature.

3. To what degree does treating periodontal disease improve glycemic control, and vice versa? What mechanisms are at work?

DR. CONWAY:

There are strong suggestions that improved periodontal care can improve glycemic control. This may be because good periodontal care and good overall oral hygiene decrease inflammatory changes in gingival tissue, which leads to diminished levels of inflammatory markers such as TNF-alpha and IL-6 that are known to increase insulin resistance. Increased levels of TNF-alpha may also worsen glycemic control.

Elevations in blood glucose lead to the formation of

glycated proteins called Advanced Glycation Endproducts (AGE). AGEs exert their effects by binding to specific cell surface receptors, such as the Receptor for Advanced Glycation Endproducts (RAGE). The interaction of AGE and RAGE induces the production of pro-inflammatory modulators such as cyclooxygenase-2 (COX-2), as well as such cytokines as TNF-alpha, IL-6 and TGF-beta, resulting in oxidative stress, inflammation and vascular dysfunction.

Increased levels of AGE proteins is in turn associated with increased levels of RAGE, which are not only highly up-regulated in poorly controlled diabetics as a result of hyperglycemia, but are also increased under conditions characterized by inflammation

or oxidative stress. Thus, we see the bi-directional relationship in this light as a vicious cycle: Poor glucose control leads to increased AGE, which in turn leads to increased inflammation via inflammatory cytokines, which exacerbates the inflammation seen with periodontal disease. The worsening periodontal disease in turn increases production of inflammatory cytokines, which increases insulin resistance and further worsens glucose control. A similar interaction takes place in diabetics' nerves and kidneys, leading to diabetic neuropathy and diabetic nephropathy, respectively.

We also know that the incidence of heart disease in diabetics is two to four times greater than that of the general population, and so the AGE-RAGE interaction may be a common link to all of the many complications of diabetes. If we block the RAGE, we can positively affect the periodontitis and these other complications.

Inflammatory cytokines are not ligands to the RAGE receptor, but they do create an environment in which they recruit and activate cells that will generate and release ligands. Although it is impractical to measure inflammatory cytokines in clinical practice, an inexpensive and highly sensitive C-Reactive Protein (CRP) assay is now available, which is covered by health plans in most provinces. This assay gives us a surrogate measure of the inflammatory burden and, together with cholesterol and blood pressure levels, refines our estimation of cardiovascular risk. Decreasing CRP levels decrease cardiovascular risk while improving insulin sensitivity. Similarly, effective treatment of periodontal disease decreases CRP levels and thus improves insulin sensitivity and glucose control.



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DR.TENENBAUM:

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A common antibiotic used to treat periodontal infection, doxycycline, has two very important side properties that should be exploited when treating a difficult periodontal disease case. First, as a tetracycline derivative, it inhibits matrix metalloproteinases (MMPs) that destroy soft and hard connective tissue around teeth. Patients with diabetes and lab animals with induced diabetes have been shown to produce higher levels of MMPs, which may help explain the correlation mechanistically.

Second, doxycycline interferes with protein glycation. We know that many proteins in the body can become overly glycated in diabetics, including hemoglobin A1c and collagen, the major connective protein in bone and gum tissue. When these proteins become glycated, they themselves activate receptors for AGE, which stimulates inflammation. So, glycated proteins actually play a role in diabetes by up-regulating the disease process. Doxycycline inhibits the glycation process not only of collagen, which, as it becomes over-glycated disrupts the remodeling and healing process, but also of proteins that, once glycated, bind to receptors that stimulate inflammation.

There are many reasons why we want to control infection – periodontal pathogenic bacteria themselves produce AGEs – but it is important that we normalize both the glycation process and the levels of MMPs so they are not causing advanced connective tissue loss. By doing so, we can also exact positive outcomes with respect to glycemic control.

4. What is the role of the dental professional in screening for diabetes?

DR.TENENBAUM:

Monitoring our patients' overall health should be a key concern. There is often a disconnect between the status of a

patient's diabetes and the degree to which they believe it is in check, and the dental team should be alert for warning signs that suggest poor control. The biggest sign is persistent periodontal disease, despite best efforts to treat it.

If we suspect that a patient's diabetes is not well controlled, a blood test for glycated hemoglobin levels will provide a snapshot of their blood sugar over the past three months. While it is not used for the purposes of actual diagnosis, it is a useful test for the dental office setting (especially a dental clinic in hospital), where we see patients who may or may not have eaten prior to their appointment, and at various times throughout the day – factors that would interfere with a fasting plasma glucose test. If the results warrant it, we can then contact the patient's physician and inform them that, based on both periodontal status and the A1c test, the patient may require more help to control their diabetes.

In my clinical experience, I've identified several undiagnosed diabetics with assessments of glycated hemoglobin via testing done in the hospital laboratory. These were patients who had reported normal blood glucose readings when tested during their routine medical checkups or by self-testing, but were revealed to have elevated levels of A1c. I have also treated patients who already had been diagnosed with diabetes and were thought to be under control given normal random blood glucose testing, but who also had high A1c levels. So it's a useful test.

Physicians should also appreciate that uncontrolled periodontal disease may be contributing to poor diabetes treatment outcomes. Oral disease is often left out of the medical equation, even though infections of the mouth have as much impact on overall health as those elsewhere in the body. To put it into perspective, the area of ulcerated, inflamed or infected tissue in the mouth of an average patient with moderately severe to severe periodontitis would roughly equate to one half of that patient's forearm.

DR. CONWAY:

The dentist should have a high index of suspicion for diabetes in the patient with unexplained or persistent periodontal disease. A random capillary glucose test can also be done quite easily in the dentist's chair and, if the result is elevated, referral can be made for further evaluation. A fasting level of greater than 6 mmol/L would be abnormal, and levels greater than 7 mmol/L would be suggestive of diabetes. Random glucose levels greater than 8 mmol/L are also abnormal and glucose levels higher than 11 are highly

suggestive of diabetes. Capillary blood glucose meters are very easy to use. The meters can usually be obtained without cost, and test strips cost about one dollar each.

5. What role can the dental professional play as part of a diabetes treatment team?

DR. CONWAY:

The dentist is a valuable and often under-appreciated member of the diabetes treatment team, which includes the physician, the diabetes specialist, the nurse educator, the pharmacist and the dietitian. Dentists frequently have long term therapeutic relationships with their patients, and are thus well placed to observe changes in oral health which may signal alterations in diabetes management.

As we have seen, worsening periodontal disease suggests that diabetic control is deteriorating and may also indicate worsening of other diabetic co-morbidities such as kidney, eye or cardiovascular disease. Improving the inflammatory state may decrease insulin resistance and improve glucose control; therefore, more frequent visits to the dental office may be indicated, as well as the creation of an appropriate oral hygiene home care regimen that includes brushing, flossing and the use of the more modern mechanized oral health systems. We recommend that non diabetics floss daily, brush for at least 2 minutes twice a day and see a dental health professional every 6 months. Because of the higher stakes in persons with diabetes more frequent flossing, brushing and dental visits may be indicated.

DR. TENENBAUM:

Beyond providing routine treatment for periodontal disease, dental professionals can augment patient care by keeping the lines of communication open. Simply asking a patient how well their diabetes has been controlled, and how often they have seen their physician, can be helpful. Reminding them of the relevance of their periodontal health is also important, as is initiating contact with the appropriate physician when necessary. All too often there is no communication within or between the silos in which health professionals tend to

work, and we leave it to the patient to communicate our concerns or suggestions. We – all health professionals – need to see ourselves as part of a larger team, and understand our roles on it. ■

Web Resources

www.cda-adc.ca
www.cap-acp.ca

www.perio.org

www.diabetesclinic.ca

www.diabetes.ca

*Canadian Dental Association
Canadian Academy of
Periodontology*

*American Academy of
Periodontology*

*Canadian website for health
professional and patient educa-
tion. Offers a free capillary
glucose test meter to dentists.
Canadian Diabetes Association*