No Sugar Coating It! The Link between Periodontal Disease and Diabetes Mellitus

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Introduction
This course seeks to improve the dental care provider's understanding of the interaction between periodontal disease and diabetes mellitus as well as aid in the clinical decision making to care for patients with diabetes mellitus and periodontal disease.

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Overview

Periodontal diseases have been associated with numerous systemic diseases and conditions, including diabetes mellitus, rheumatoid arthritis, cardiovascular diseases, and obesity. Diabetes mellitus is a clinically and genetically heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids, and proteins.\textsuperscript{1,2}

The defining feature of diabetes is abnormal elevation in blood glucose levels, caused either by an insufficient secretion of insulin by the pancreatic β-cells and/or insulin resistance in liver and muscle cells.\textsuperscript{3} The long-term hyperglycemia that results from this disorder can lead to damage of various end organs including the heart, eyes, kidneys, nervous system, vascular system, and periodontium.\textsuperscript{2,3} Diabetes mellitus and periodontitis share common risk factors and present unique challenges for oral health care providers who are treating patients with both diseases.

This course seeks to improve the dental care provider’s understanding of the interaction between periodontal disease and diabetes mellitus as well as aid in the clinical decision making to care for patients with diabetes mellitus and periodontal disease.

Learning Objectives

Upon completion of this course, the dental professional should be able to:

• Understand the current scientific literature about the association between periodontal health and diabetes and discuss the interactions between these two conditions with patients.
• Be an active participant in an interdisciplinary team of health care providers treating patients with diabetes mellitus and periodontal disease.
• Evaluate patients' risk factors and treatment needs based upon individualized patient needs and glycemic control.
• Discuss with patients the common risk factors associated with periodontitis and diabetes and be familiar with strategies to treat those risk factors.
• Discuss with interdisciplinary colleagues the importance of and effective methods for treatment of periodontal disease in patients who have diabetes mellitus.

Introduction

Diabetes mellitus is a group of metabolic syndromes characterized by a disordered metabolism and abnormally high blood sugar (hyperglycemia) resulting from low levels of the hormone insulin with or without insulin resistance.\textsuperscript{3} Approximately 29.1 million people in the United States (9.3%) are estimated to have diabetes with 21.0 million of those being diagnosed.\textsuperscript{4}
Incidence of has more than doubled since 1998, when 800,000 new cases were diagnosed. By comparison, in 2012, 1.7 million new cases were diagnosed. Diabetes mellitus has been linked to poor oral health and nutritional habits, which have dramatically increased over the past few decades.\textsuperscript{2,4,6}

Periodontitis is initiated by infectious agents resulting in tissue destruction caused by host inflammation within the supporting structures of the teeth.\textsuperscript{7,8} It has been shown to have an association with numerous systemic conditions in a bidirectional manner.\textsuperscript{9} The inflammatory burden and immune cell dysfunction seen in both periodontitis and diabetes mellitus can alter treatment recommendations and therapeutic outcomes for patients with both periodontitis and diabetes mellitus.\textsuperscript{10} Due to the number of individuals affected by both periodontal disease\textsuperscript{11} and diabetes mellitus,\textsuperscript{4} the understanding of the interaction between periodontal disease and diabetes mellitus is of utmost importance to the dental practitioner.

Epidemiology and Classification of Diabetes Mellitus
Diabetes can be classified into these four general categories: 1) Type 1 diabetes, which is due to β-cell destruction and usually leads to a complete lack of insulin, 2) Type 2 diabetes (the most common form of diabetes mellitus), which is due to a progressive defect in insulin secretion as well as cellular insulin resistance, 3) Gestational diabetes, which is typically diagnosed during the 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester of pregnancy and resolves after birth, and 4) diabetes due to other systemic diseases and conditions (e.g., monogenic diabetes syndromes, diseases of the endocrine pancreas, and drug or chemical induced diabetes).\textsuperscript{3} Additionally, some individuals have glucose levels that do not meet the criteria for diabetes, but are elevated compared to normal levels. The conditions may be labeled “prediabetes,” which includes both impaired fasting glucose (IFG) and impaired glucose tolerance (ITG).\textsuperscript{3} These individuals may have elevated blood glucose only in specific circumstances. IFG, ITG, and gestational diabetes are strong predictors for future development of Type 2 diabetes mellitus, and IGT is a significant predictor for myocardial infarction and stroke.\textsuperscript{12,13}

Diagnosis of diabetes mellitus in adults can be based on 2 different lab tests. Plasma glucose, which may be tested either fasting or 2 hours after a 75g oral glucose tolerance test (Table 1), shows current glycemic control.\textsuperscript{14,15} The use of glycated hemoglobin, or HbA1c, in clinical treatment of patients with diabetes allows the practitioner to estimate the average glucose level over the 30-90 day period preceding the test. It does not account for short-term fluctuations in plasma glucose, but may allow for an overall assessment of glycemic control (Table 2).\textsuperscript{16} An additional advantage of HbA1c

| Table 1. Diagnostic Criteria for Diabetes Mellitus, IGT, and IFG.\textsuperscript{3} |
|----------------------------------|------------------|----------|----------|
|                                  | Normal           | Diabetes | IGT      | IFG      |
| Fasting plasma glucose (mg/dl)   | <100             | ≥126     | 100-125  |
| Casual plasma glucose (mg/dl)    | ≥200 plus        |          |          |
| symptoms of diabetes             |                  |          |          |
| 2-hour postload glucose (OGTT)   | <140             | ≥200     | 140-199  |
| HbA1c                            | <5.7%            | ≥6.5%    | 5.7-6.4% |
|                                  |                  |          | 5.7-6.4% |
Periodontitis is a chronic disease of the hard and soft tissue supporting the teeth caused by bacterial plaque resulting in progressive destruction of the periodontal ligament and alveolar bone. The disease typically has a slow to moderate rate of disease progression, but periods of accelerated attachment loss may be associated with local and/or systemic factors. Disease severity is classified as mild (1-2mm), moderate (3-4mm), or severe (≥ 5mm) based on the amount of clinical attachment loss (CAL). The prevalence of periodontitis has been estimated to be over 47% of U.S. adults, or 64.7 million individuals. Of those individuals, 8.7% showed mild disease, 30.0% demonstrated moderate disease, and 8.5% had severe chronic periodontitis. Risk indicators for periodontitis include male gender, Hispanic ethnicity, cigarette smoking, uncontrolled or poorly controlled diabetes mellitus, and lower socioeconomic status. Prevalence of periodontitis varied two-fold between the lowest and the highest levels of socioeconomic status (Figure 2).
Disease progression of periodontitis has been categorized into subpopulations demonstrating rapid progression (10-15% of disease cases), moderate progression (80% of disease cases), and mild/no progression (5-10% of disease cases).\textsuperscript{19,27,28} The prevalence distribution of periodontal disease severity and disease progression in treated and untreated populations\textsuperscript{19} suggests that host factors may play the larger role in disease progression after bacterial initiation.\textsuperscript{30-35}

**Diabetes Influence on the Periodontium**
Current evidence suggests diabetes is a risk factor for gingivitis and periodontitis and that the level of glycemic control is an important
Determinant in this relationship. Diabetes has been associated with an increased risk of periodontitis in children, in populations with high incidence of diabetes mellitus, and in adult populations. In a multivariate risk analysis, subjects with diabetes demonstrated an approximately 3-fold increased odds of having periodontitis compared to healthy subjects after adjusting for confounding factors including age, gender, and oral hygiene. Additionally, diabetic subjects with poor glycemic control demonstrated greater progressive bone loss as compared with subjects with diabetes who are well-controlled. Periodontitis has been referred to as the “sixth complication of diabetes” indicating that much like the classic complications of diabetes, periodontitis may be a result of the extended hyperglycemia on the periodontal tissues.

Periodontal Disease Effects on Diabetes
The presence of periodontal disease indicates an increased risk of worsening glycemic control over time. Furthermore, subjects with both diabetes and periodontitis have shown to have higher rates of complications and higher mortality rates than diabetic subjects without periodontitis. There is a biologic rationale that could explain an influence of periodontal disease on diabetic status. Periodontitis patients have been shown to have an increase in serum pro-inflammatory markers when compared to subjects without periodontitis; these include including C-reactive protein (CRP), IL-6, and fibrinogen. Furthermore, patients with periodontitis have also been shown to experience high levels of bacteria and endotoxins entering the bloodstream through seemingly harmless activities such as chewing. This dissemination of bacteria associated with periodontitis may play a role in the influence of periodontal disease on diabetes mellitus. Acute bacterial and viral infections have been shown to increase insulin resistance in non-diabetic patients and chronic gram negative periodontal infections may also result in increased insulin resistance and worsening glycemic control.

However, there is a controversy about how to interpret this information. The questions remains whether there is an underlying mechanism that affects both disease processes, or whether one condition will actually cause the other to worsen. In non-diabetic patients, severe chronic periodontitis was associated with a 5-fold greater increase in HbA1c over the 5 year study period compared to subjects without diabetes, indicating periodontitis might play a role in increasing hyperglycemia that could potentially increase the risk of developing diabetes. However, in a prospective study patients with moderate to severe periodontitis demonstrated an increased risk of developing diabetes, but the association was not significant after adjusting for common risk factors such as smoking, sex, BMI, hypertensive status, and lipid profiles. A systematic review of the best data available found relatively weak evidence supporting adverse effects of periodontal disease upon glycemic control in diabetic patients. The authors did caution that better and longer term studies are needed to confirm the significance of this cause and effect relationship.

Proposed Mechanisms of Interaction between Periodontal Disease and Diabetes Mellitus
Diabetes and periodontitis both involve significant dysregulation of the immune system. Periodontal tissue breakdown occurs in response to bacterial stimuli as a result of host inflammatory response. Periodontal tissue breakdown seen in disease is mediated by pro-inflammatory cytokines and mediators. There are significant differences in the inflammatory response among individuals, which influences susceptibility to disease as well as severity of disease progression. The immunologic dysregulation seen in diabetes is associated with both metabolic and physiologic changes in tissues. The most significant are hyperglycemia leading to the formation of AGEs as well as hyperlipidemia. Furthermore, diabetic subjects have an increased hyperinflammatory state and demonstrate increased serum levels of pro-inflammatory cytokines. As pro-inflammatory cytokines increase, patient’s glycemic control gets worse in a dose-dependent manner. Common pro-inflammatory biomarkers implicated in both periodontal disease and diabetes mellitus include interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), prostaglandin E₂ (PGE₂), receptor
activator of nuclear factor kappa B ligand (RANKL), and matrix metalloproteinases (MMPs).

Because inflammation is central to the pathophysiology of both periodontitis and diabetes, the role of inflammatory mediators in the interaction is critical and a summary of some of the key mechanisms will be discussed (Figure 3).

**Advanced Glycation End Products (AGEs) and the Influence on the Immune Response**

Patients with poor glycemic control have an average higher blood sugar as opposed to patients without diabetes. One result of increased blood sugar over time is a nonenzymatic glycation of many proteins throughout the body, known as Advanced Glycation Endproducts, or AGE’s. AGEs occur at an increased rate when patients are hyperglycemic, and have direct effects on both pro-inflammatory mediators as well as bone metabolism. They have been shown to increase pro-inflammatory cytokines through their interaction with the receptor for AGE (RAGE). Furthermore, AGE levels locally in periodontal tissues and in the systemic circulation have been linked to an increased periodontal inflammatory state and more advanced periodontitis in patients with type 2 diabetes. Therefore, it is clear that AGE-RAGE interactions are important in the pathogenesis of periodontal disease in patients with diabetes. RAGE activation leads to an exaggerated inflammatory response and increased tissue destruction that is typical of periodontitis in diabetic patients. This interaction may also account for the relationship between glycemic control and periodontal destruction observed in epidemiologic studies.

**Patient-related Modifying Factors of Periodontal Disease and Diabetes and Their Interactions**

Periodontal disease and diabetes share many risk factors and risk modifiers, including obesity, hyperlipidemia, and smoking. Recent evidence may suggest that obesity, and the inflammation associated with adipose tissue, may be a modifying factor in this relationship (Figure 4). Obesity has also been shown to negate the effects of nonsurgical periodontal treatment on systemic CRP levels in patients with at least mild chronic periodontitis. The modifying affect of obesity on the relationship between periodontitis and diabetes may account for the inconsistent results of some interventional trials and may provide positive outcomes for patients with diabetes and periodontitis.
insight into the management of diabetic patients in a dental office as well as indications for dental screening recommendations for diabetic and prediabetic patients under management of a physician.

**Periodontal Therapy in Patients with Diabetes**

Clinical and microbiologic responses to periodontal therapy depend on the patient’s diabetic status. Well-controlled diabetic patients respond to therapy similar to non-diabetic patients. In patients with moderate and poorly controlled diabetes, varying results have been reported. Some studies report achieving a mild reduction in glycemic index after periodontal therapy, while the largest randomized controlled study performed to date shows no change in HbA1c in response to periodontal therapy. The best evidence to date shows that if an effect occurs, it does not last beyond 3-4 months after therapy without further interventions. However, the variability in this response to therapy may relate to some of the comorbidities of diabetes, including obesity and cardiovascular disease, which may alter response to therapy. There is cross-sectional data to suggest that periodontal treatment is associated with a reduction in HbA1c and decreased overall medical expenses in a large cohort (> 5000 patients) of individuals. The mechanism of this interaction, however, remains unclear and may simply indicate that those patients who sought dental treatment were overall more committed to healthy lifestyle changes that improved their overall health and glycemic control.

**Clinical Decision Making for Treatment of Patients with Periodontal Disease and Diabetes in a Dental Setting**

Caring for patients with both diabetes and periodontitis requires careful evaluation, quantification and ongoing monitoring of existing periodontal inflammation. Consultation with the patient’s physician in regards to current levels of glycemic control and future diabetes management is an important aspect of their overall medical management. Additionally, given the large number of undiagnosed diabetic patients, dental healthcare providers must be aware of the signs and symptoms of diabetes to make appropriate referrals when indicated. Patients with diabetes may also require additional evaluations and treatment for comorbid diseases, such as obesity and cardiovascular disease. Since conventional therapies are not always as effective in diabetic patients as on unaffected patients, adjunctive therapies should be considered. The addition of adjunctive antibiotic therapy in diabetic patients has been shown to increase the effect of periodontal therapy on...
glycemic control in some diabetic patients. Therefore, antibiotics may be considered during both active therapy and maintenance to improve results of periodontal therapy.

**Summary**
Both periodontal disease and diabetes are multifactorial diseases that have many comorbidities and have been shown to increase host inflammatory burden. Diabetes is also associated with other dental conditions and diseases, including xerostomia (dry mouth), dental caries, and oral candidiasis. Good oral health is integral to optimal overall health and quality of life, but the interactions between systemic and oral health may not be the primary focus of physicians and other healthcare providers. Therefore, dental

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**Figure 5.** Risk Factors Associated with Diabetes and Periodontitis to Consider during Periodontal Therapy.
healthcare providers should be aware of the burden and risks of diabetes and its oral manifestations, including rapid periodontal disease progression and make appropriate referrals when indicated. Likewise, patients who have been diagnosed with diabetes mellitus should be carefully questioned about their glycemic control and overall oral health status. Periodontal disease and the inflammatory burden it creates should be discussed with patients and the use of advanced therapies and/or more stringent maintenance protocols to control the increased inflammatory load in patients with both diabetes and periodontitis should be considered.

Comanagement of patients with diabetes and periodontal disease will promote better dental and medical care for patients. Appropriate diagnoses and communication between practitioners will allow for patient screening for additional comorbidities, which will lead to earlier detection and treatment. This information can also characterize the patients’ overall glycemic control which will allow for personalization of treatment plan and maintenance protocols.

In the dental office, patients’ glycemic control should be monitored to ensure that a medical emergency from hypo- or hyperglycemia does not occur. Counseling patients about the effects that their diabetes may have on their oral condition is also an important step in encouraging patients to optimally control their diet and/or medications to maintain a healthy level of glycemic control, which can improve their overall and oral health.
Course Test Preview
To receive Continuing Education credit for this course, you must complete the online test. Please go to: www.dentalcare.com/en-us/professional-education/ce-courses/ce520/start-test

1. **Diabetes mellitus** is a group of metabolic diseases all of which present with ___________.
   A. insulin resistance
   B. high blood sugar (hyperglycemia)
   C. faulty insulin production
   D. All of the above.

2. Approximately _____ of U.S. adults have diabetes.
   A. 4%
   B. 6%
   C. 9%
   D. 15%

3. The most common form of diabetes, which is due to a progressive defect in insulin secretion as well as cellular insulin resistance, is ___________.
   A. Type 1 diabetes
   B. Type 2 diabetes
   C. Gestational diabetes
   D. Diabetes due to systemic diseases

4. “Prediabetes” consists of two types of abnormally elevated glucose levels that do not reach the threshold for diabetes mellitus. These are ___________.
   A. impaired Fasting Glucose (IFG) and Impaired Glucose Tolerance (IGT)
   B. impaired Free Glucose (IFG) and Impaired Glucose Testing (IGT)
   C. impaired Glucose Function (IGF) and Impaired Typical Glucose (ITG)
   D. impaired Glucose Trends (IGT) and Insulin Function Transformation (IFT)

5. A diagnosis of diabetes may be made if a patient’s hemoglobin A1c (HbA1c) is ____.
   A. <5.7%
   B. 5.7-6.4%
   C. ≥6.5%
   D. >8%

6. The American Diabetes Association (ADA) recommends testing overweight or obese adults who have one or more risk factors for diabetes and all overweight and obese patients 45 years of age and older __________ to identify diabetes and prediabetes diagnoses.
   A. before age 60
   B. every 10 years
   C. every 5 years
   D. yearly
7. In a patient with diabetes whose HbA1c levels were approximately 8%, this correlates to an average blood glucose level of 210 mg/dl.

The American Diabetes Association (ADA) recommends physician intervention to improve glycemic control for patients with an HbA1c over 8%.

A. The first statement is true, the second statement is false.
B. The first statement is false, the second statement is true.
C. Both statements are true.
D. Both statements are false.

8. Diabetes prevalence in the U.S. has increased approximately 2-fold between 1994 and 2014 and this increase follows obesity trends in the United States.

A. True
B. False

9. Risk indicators for periodontal disease include all of the following EXCEPT ____________.

A. uncontrolled or poorly controlled diabetes mellitus
B. male gender
C. cigarette smoking
D. All of the above are risk indicators for periodontal disease.

10. Overall, research indicates that patients with diabetes have a ____-fold greater risk of developing periodontitis than their nondiabetic counterparts.

A. 1
B. 2
C. 3
D. 5

11. Periodontitis has been referred to as the “sixth complication of diabetes” and worsening glycemic control is associated with higher rates and more significant destruction of periodontal structures.

A. True
B. False

12. Patients with periodontitis and diabetes ____________ when compared with diabetic patients without periodontitis.

A. have a higher risk for worsening glycemic control over time
B. have a higher risk for diabetic complications
C. have a higher mortality rate
D. All of the above.

13. Both diabetes mellitus and periodontal disease involve a significant dysfunction of the immune system. In diabetic patients the nonenzymatic addition of glucose to proteins, produces advanced glycation end products (AGEs), which activate receptors (RAGE) and upregulate pro-inflammatory mediators.

A. True
B. False
14. Current studies indicate that periodontal therapy may result in __________ medical costs based upon insurance data in a large cohort.
   A. increased
   B. decreased
   C. similar

15. In patients with diabetes and periodontitis, adjunctive periodontal treatments and management of comorbid conditions, should be encouraged for optimal overall and oral health.
   A. True
   B. False
References


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Dr. Geisinger is an Associate Professor at the University of Alabama at Birmingham (UAB) in the Department of Periodontology where she teaches a broad range of classes and serves as the Director of the Advanced Education in Periodontology Program. She received her Bachelor's of Science in Biology from Duke University graduating cum laude and completed her dental training at Columbia University College of Dental Medicine. She completed her Certificate in Periodontology and Master's of Clinical Science at the University of Texas Health Science Center in San Antonio. Dr. Geisinger is a Diplomate in the American Board of Periodontology. In her role at UAB, she is involved in clinical and translational research examining the interactions between periodontal diseases and systemic health. Her research focuses on periodontal-systemic interactions, periodontal regenerative therapies, implant dentistry, and educational technology. She is a member of the ADA, AAP, SAP, ADEA, AADR/IADR, AAWD, AAUW, and the President-elect of the AAPF.

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Dr. Matthew Rasmussen pursued his undergraduate studies at the University of Florida, graduating Cum Laude. After his undergraduate education, he moved to Birmingham, Alabama and received his doctor of dental medicine from the University of Alabama at Birmingham.

Subsequent to his dental school training, Dr. Rasmussen completed a General Practice Residency program at the University Hospital in Birmingham, Alabama. He then completed post-graduate training at the University of Alabama’s Post Graduate Periodontal Residency program. During his final year of residency, he served as the Chief Resident, awarded to only Thone resident in the program each year. He is currently practicing in Tampa, Florida at Implant and Periodontal Therapy and is a Board Eligible Periodontist.

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