

Bidirectional association between diabetes mellitus and inflammatory periodontal disease.

A review

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Background. Diabetes mellitus is a metabolic disorder characterized by hyperglycemia. The abnormal glucose metabolism results from defects in insulin production or insulin action, or both. For decades, it was suspected that diabetes contributed to poorer oral health and the increased frequency of periodontitis. More recently it was found that periodontitis could adversely affect glycemic control in diabetics. This review focuses on the bidirectional relationship between diabetes mellitus and periodontitis.

Methods and Results. A review of the literature on periodontal disease in diabetes using the following key words: periodontitis/periodontal disease and diabetes mellitus, hyperglycemia/glycemic control.

Conclusions. There is strong evidence for an association between diabetes mellitus and inflammatory periodontal disease. Diabetes mellitus increases the risk for and severity of periodontitis, and periodontal diseases can aggravate insulin resistance and affect glycemic control. Periodontal treatment improves glycemic control in type 2 diabetics; control of periodontal infection is not only important for oral health, it may also improve overall health.

Key words: diabetes mellitus, periodontitis, hyperglycemia, glycemic control, periodontal treatment

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disease, characterized by hyperglycemia due to a defect in insulin secretion by pancreatic β cells, a decrease in insulin sensitivity, or a combination of both¹. The current classification of diabetes is based upon the pathophysiological mechanisms of each form of the disease^{1,2}. Type 1 diabetes results from autoimmune destruction of pancreatic β cells, typically leading to a complete loss of insulin secretion. This form is usually present in children and adolescents. The lack of insulin production in patients with type 1 diabetes makes the use of exogenous insulin necessary to sustain life, hence the former name "insulin-dependent diabetes" (ref.²). Type 2 diabetes, previously called non-insulin dependent diabetes, results from insulin resistance, which alters the availability of endogenously produced insulin in the target cells^{1,2}. Type 2 diabetic patients can be undiagnosed for many years as the hyperglycemia appears gradually and often without symptoms³.

Gestational diabetes usually has its onset in the third trimester of pregnancy, and adequate treatment reduces perinatal morbidity. Most women with gestational diabetes return to a normoglycemic state after parturition; however, a history of gestational diabetes significantly increases the risk of subsequently developing type 2 diabetes⁴.

Periodontal disease (PD) is a chronic inflammatory disease of the tissues that support and attach the teeth

to the jaws⁵. Although it is initiated and maintained by a mixed endogenous gram-negative bacterial infection, the onset and progression of the disease is a result of the inflammatory host response. PD is characterized by gingival inflammation, periodontal pocket formation, loss of connective tissue attachment, and alveolar bone resorption, ultimately resulting in tooth loss⁶⁻⁸.

The relationship between diabetes mellitus and periodontitis has appeared in the literature for over 70 years; however, with conflicting data. Numerous studies in various populations have demonstrated that individuals with diabetes tend to have a higher prevalence of and more severe periodontitis than nondiabetics⁹. Periodontal disease is the most prevalent oral complication in patients with type 2 DM (ref.^{10,11}). In a classic cross-sectional study, type 1 diabetes has been associated with a fivefold increased prevalence of periodontitis in teenagers¹² and with greater bleeding index, probing pocket depth and clinical attachment level^{13,14}. Today, chronic periodontitis has been identified as the sixth complication of diabetes alongside retinopathy, nephropathy, neuropathy, macrovascular disease and poor wound healing¹⁵.

Link between diabetes mellitus and inflammatory periodontal diseases: data from epidemiological studies

Diabetes mellitus and periodontal diseases are both chronic, common, multifactorial diseases in the population, especially in those over 60 years of age, and are related.

An overall assessment of the available data strongly suggests that diabetes is a risk factor for gingivitis and periodontitis^{16,17}. Cianciola et al. reported the higher prevalence of gingival inflammation and periodontitis in children with type 1 diabetes than in children without diabetes who had similar plaque levels¹².

Ervasti and colleagues observed greater gingival bleeding in patients with poorly controlled diabetes compared to nondiabetics or subjects with well-controlled diabetes¹⁸. Patients with type 2 diabetes also had greater gingival inflammation than control subjects without diabetes; the highest level of gingivitis was found in patients with poor glycemic control¹⁹.

A multivariate risk analysis showed that patients with type 2 diabetes had approximately threefold increased odds of having periodontitis compared to those without diabetes, after adjusting for confounding variables including age, sex and oral hygiene measures^{10,11}.

Papapanou et al. performed a meta-analysis of studies conducted before 1996 that included more than 3,500 adults with diabetes; they revealed a significant association between diabetes and periodontitis¹⁶. Another two-year longitudinal study demonstrated a fourfold increased risk of progressive alveolar bone loss in adults with type 2 diabetes compared with those without this disease. Other meta-analyses indicated a statistically significantly higher mean clinical attachment loss (CAL) of 1 mm ($P=0.02$, 95% CI: 0.15-1.84) and a greater mean probing depth of 0.46 mm ($P=0.05$, 95% CI: 0.01-0.91) in patients with type 2 diabetes mellitus compared with controls. It can be summarized that poor glycemic control in patients with diabetes is associated with an increased risk of progressive loss of periodontal attachment and alveolar bone^{20,21}.

Although most research on the relationship between diabetes and periodontal disease has focused on mechanisms by which diabetes may affect periodontal status, a growing body of evidence has also examined the converse relationship; namely, how periodontal diseases may affect the metabolic state.

Taylor et al. demonstrated a sixfold increased risk of worsening glycemic control in patients with type 2 diabetes who had severe periodontitis compared with that in subjects with type 2 diabetes who did not have periodontitis²².

Some studies have shown that the combination of scaling and root planing with systemic doxycycline therapy is associated with an improvement in periodontal status that is accompanied by significant improvement in glycemic control, as measured by the glycated hemoglobin assay (HbA1c) (ref.^{23, 24}).

A meta-analysis of 10 intervention trials that included more than 450 patients found an average decrease in absolute HbA1c values of about 0.4 percent after scaling and root planing²⁵.

However, this value was not statistically significant. Moreover, several other meta-analyses have indicated that nonsurgical treatment of periodontitis in patients with type 2 diabetes has a beneficial effect on their glucose condition²⁶⁻²⁸. Despite the variation in these studies, the results were similar, with a significant decrease in glycated

hemoglobin level of 0.4-0.7% in the periodontally treated group. The studies also noted a lack of sufficient data for this effect in children with type 1 diabetes mellitus.

Therefore, further research is required to determine how variations in clinical responses after periodontal therapy might be reflected in changes, or a lack of changes, in glycemic control.

Effects of diabetes on periodontium

Inflammation is a central feature of both diabetes and periodontal disease, and inflammatory processes are up-regulated in periodontal tissues in diabetic patients. There is a wide range of mechanisms by which diabetes adversely affects the periodontium and, vice versa, how periodontitis influences control of diabetes.

In general, the mechanisms that explain the classic microvascular and macrovascular complications of diabetes are also true for the periodontium. The periodontium is a richly vascularized organ, similar in many aspects to the retina and the glomerulus. Thus, accumulation of advanced glycation end products (AGE) and their effects on cell-to-matrix and matrix-to-matrix interactions, increased tissue oxidant stress, altered endothelial cell function and elevated activity of matrix metalloproteinases. Similar changes seen in the tissues affected by the classic diabetic complications also occur in the periodontal tissues. In humans, the levels of AGE products in serum were associated with the extent of periodontitis in adults with type 2 diabetes²⁹. In a mouse model, diabetic animals exhibit increased expression of receptors for advanced glycation end-products (RAGE), and treatment with soluble RAGE decreased the levels of proinflammatory cytokines and suppressed alveolar bone loss³⁰.

However, the periodontium differs from other tissues and organs, as previously mentioned in that the periodontium undergoes constant wounding from the bacterial biofilm. Diabetes results in changes in the function of immune cells including neutrophils, monocytes and macrophages³¹.

Neutrophil adherence, chemotaxis and phagocytosis are often impaired, enabling bacteria to persist in the periodontal pockets and to significantly increase periodontal destruction. In addition, patients with diabetes have increased apoptosis, which is associated with prolonged wound healing³². Conversely, the monocyte-macrophage cell line may be hyperresponsive to bacterial antigens in people with diabetes, resulting in significantly increased production of pro-inflammatory cytokines and mediators^{31,33}.

Salvi et al. found that peripheral blood monocytes from individuals with diabetes demonstrate upregulated production of TNF- α in response to antigens from the gram-negative, anaerobic periodontal pathogen *Porphyromonas gingivalis*, compared to monocytes from people without diabetes³⁴. Both type 1 and type 2 diabetes mellitus are also associated with elevated levels of systemic markers of inflammation³⁵.

These host defense alterations and the increased levels of proinflammatory mediators in diabetes result in increased periodontal inflammation, and also contribute

to poor diabetes metabolic control, explaining thus, in part, the bidirectional relationship of these two diseases.

Effects of periodontitis on diabetes

On the other hand, the presence of periodontal diseases can have a significant impact on the metabolic state in diabetes. Periodontitis is also associated with an increased risk for diabetic complications. In a study by Thorstensson et al., 82% of diabetic patients with periodontitis experienced one or more major cardiovascular, cerebrovascular or peripheral vascular events during the study period of 1-11 years, compared to only 21% of diabetic people without periodontitis³⁶. Saremi et al. examined the effect of periodontal disease on mortality in more than 600 subjects with type 2 diabetes. After accounting for other known risk factors, the death rate from ischemic heart disease was 2.3 times higher in people with severe periodontitis than in patients without periodontitis or with only mild periodontitis, while the death rate from diabetic nephropathy was 8.5 times higher in those with severe periodontitis³⁷.

Periodontal treatment usually consists of the debridement of root surfaces to remove bacterial plaque biofilms and mineralized plaque (i.e. calculus). Such debridement, called scaling and root planing, can be done using a non-surgical approach or following surgical reflection of soft tissue flaps to allow visual and physical access to the root surfaces and alveolar bone.

In some cases, especially in patients with aggressive periodontitis, systemic antibiotics are used as an adjuvant therapy. In people with diabetes, the tetracycline class of antibiotics has most frequently been used since the tetracyclines are known to decrease production of matrix metalloproteinases such as collagenase, in addition to their antimicrobial effects^{31,38}.

CONCLUSIONS

There is strong evidence for an association between diabetes mellitus and inflammatory periodontal diseases. Diabetes mellitus increases the risk for and severity of inflammatory periodontal diseases. Biologically plausible mechanisms have been demonstrated in abundance.

The impact of periodontal disease on glycemic control in diabetes and the mechanisms through which this occurs are less clear. It is possible that periodontal diseases may serve as accelerators of insulin resistance, and in this way lead to aggravating glycemic control. There is emerging evidence that periodontal treatment improves glycemic control in patients with type 2 diabetes; i.e. control of periodontal infection seems not only important for oral health, but may also improve the overall health of patients with diabetes mellitus. Further research is needed to clarify this aspect of the bidirectional relationship between periodontal diseases and diabetes. There is very important complex medical care in these patients and patients should be asked by physicians whether or not they have seen a dentist in the past 6-12 months. If not, physicians should recommend that patients with diabetes

seek a thorough periodontal evaluation by a general dentist or periodontist. Once again, until more evidence is available, periodontitis should be regarded as a modifiable risk factor in diabetic patients.

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AUTHORSHIP CONTRIBUTIONS

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CONFLICT OF INTEREST STATEMENT

The authors stated that there are no conflicts of interest regarding the publication of this article.

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