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Type 1 Diabetes and Periodontal Health

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ABSTRACT

It is well established that hyperglycemia affects periodontal outcomes. A body of evidence, predominantly over the past 20 years supports significant independent associations between periodontal disease and glycemic control or complications of diabetes. Association between periodontal tissue and hyperglycemia is possible through altered cellular immunity, increased proliferation of bacteria, microangiopathy, and formation of the advanced glycation end products. However, most studies focus solely on patients with type 2 diabetes or diabetes in general. There is still the paucity of data concerning patients with type 1 diabetes (T1D). Here, the authors consider the possible mechanisms linking periodontal disease with diabetes, focusing mainly on T1D and discuss possible diagnostic and therapeutic approaches. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: chronic complications of diabetes, periodontal disease, periodontal health, type 1 diabetes.

INTRODUCTION

It is well established that hyperglycemia affects periodontal outcomes. A body of evidence, predominantly over the past 20 years supports significant independent associations between periodontal disease and glycemic control or complications of diabetes. Association between periodontal tissue and hyperglycemia is possible through altered cellular immunity, increased proliferation of bacteria, microangiopathy, and formation of the advanced glycation end products.[1] However, most studies focus solely on patients with type 2 diabetes (T2D) or diabetes in general. There is still the paucity of data concerning patients with type 1 diabetes (T1D).

In this commentary the authors consider the possible mechanisms linking periodontal disease with diabetes, focusing mainly on T1D and discuss possible diagnostic and therapeutic approaches.

BIDIRECTIONAL RELATIONSHIP OF PERIODONTAL HEALTH AND DIABETES

Diabetes is a group of metabolic diseases characterized by hyperglycemia that results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. The presence of impairment of insulin secretion does not exclude the possible defects in insulin action; therefore, these 2 pathologic processes may be found in the same patient. Traditional classification of diabetes comprises 4 categories: T1D, T2D, gestational diabetes, and specific types of diabetes due to other causes.[2] T2D accounts for ~90% of all diabetes and is characterized by relative insulin deficiency and peripheral insulin resistance commonly associated with excessive weight. T1D accounts for ~5% of persons with diabetes and results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas and absolute insulin deficiency. Various autoantibodies against specific islet cells, autoantigens, may be detected in the early stages of the disease. In addition, the disease has strong human leukocyte antigen associations, with linkage to the *DQA*, *DQB*, and the *DRB* genes. It is probably environmental factors that are responsible for the observed increase in incidents of T1D. Irrespective of type of diabetes, chronic exposure to hyperglycemia leads to development of the neurovascular complications of diabetes such as retinopathy, chronic kidney disease, or

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neuropathy, major contributors to end-stage renal disease or blindness. Patients diagnosed with diabetes are also at higher risk of developing periodontal disease, among which gingivitis and periodontitis constitute the 2 main clinical forms. Both pathologic processes of periodontium are common in populations worldwide and are not limited to patients diagnosed with diabetes. Gingivitis is a reversible inflammatory disease that affects gingival connective tissue and epithelium. The experimental gingivitis studies from 1960s produce the universal principle that the biofilm is essential to the initiation of gingivitis and, if not removed, would lead to periodontitis. Periodontitis affects the supporting tissues of the teeth with progressive attachment loss and bone destruction[3] and is characterized by local destruction due to the inflammatory host response triggered by an infection with periopathogens.[4,5] It is now accepted that dental plaque accumulation is not the sole risk factor for periodontal disease, and it is not the only connection between periodontal disease and diabetes. It seems that more attention should be paid to the bacterial profile in gingivitis, and relations in which chronic, low-grade inflammation such as in the case of diabetes may predispose to the initiation of inflammation-mediated periodontal disease.[6] The incidence of chronic gingivitis is significantly higher in patients with T1D than in the healthy population and it increases with age.[1] Interestingly in a clinical trial on experimental gingivitis induced by refraining from oral hygiene for 3 weeks, no differences were found in the plaque index scores or in the composition of bacterial plaque between the patients with T1D and healthy volunteers, but the former group responded to plaque irritation by an earlier and more severe gingival inflammation, which corresponded with significantly higher levels of some inflammatory biomarkers in crevicular fluid.[7] Evidence is also emerging for an independent association between periodontitis and incident diabetes and prediabetes state.[8] In addition, evidence indicates that periodontitis adversely affects glycemic control and worsens complications of diabetes,[1,9,10]

PATHOMECHANISMS LINKING DIABETES AND PERIODONTAL DISEASE

A number of mechanisms have been proposed to explain the associations between diabetes and periodontal status, and these can be considered as alterations in the vascular, cellular, and repair processes of the host. The duration of hyperglycemia and its severity are found to be the 2 main risk factors for the development of chronic complications of diabetes. High concentrations of glucose act as a cell and extracellular matrix proliferative factor. Glucotoxicity results in exacerbation of oxidative stress, inflammatory response, insulin resistance, and protein glycation.[11] The chemical reactions involved in glucose metabolism in the hyperglycemic environment are the source of high-dose free oxygen radicals, which contribute to tissue destruction.[12] At the cellular level chronic hyperglycemia and concurrent dyslipidemia trigger alternative glucose metabolic pathways such as polyol- or hexosamine pathway and the activation of protein kinase C (PKC) and nonenzymatic protein glycation. Hyperactive polyol pathway consumes nicotinamide adenine dinucleotide phosphate (NADPH) in the aldose reductase reaction and reduces NAD^+ in the sorbitol reductase reaction and adversely affects cellular homeostasis because NADPH is necessary to maintain glutathione, the primary intracellular antioxidant, in its reduced state.[13] Monea et al[14] in the histologic study of periodontal tissues from patients with T2D revealed elevated levels of the malondialdehyde and decreased levels of glutathione compared with healthy volunteers and thus confirmed the role of oxidative stress in periodontal inflammation in diabetes. PKC is a ubiquitously expressed enzyme that participates in a wide range of intracellular signaling. The activity of particular isoforms of PKC is upregulated in vascular tissue in diabetes and is associated with development of microvascular complications.[15,16] The activation of PKC-α and PKC-δ in human gingival fibroblasts stimulates secretion of proinflammatory cytokines, tumor necrosis factor (TNF)-α and interleukin (IL)-1β, by inducing toll-like receptor 2 pathway; therefore, PKC is involved in sustaining chronic inflammation in the periodontium.[17,18] Modification of extracellular and intracellular proteins by glucose results in the formation of advanced glycation end products (AGEs), which are resistant to enzymatic degradation. The accumulation of AGEs can alter protein structure or function, trigger a range of cellular responses, promote vascular complications, and stimulate secretion of inflammatory cytokines, collagenases, and several growth factors.[19,20] Many of the effects of AGEs are receptor dependent and involve a multiligand member of the immunoglobulin