Advanced Glycation End Products, the Hidden Bridge between Diabetes and Periodontitis - A Review

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Abstract

An association between oral infections and systemic diseases especially diabetes mellitus has been suspected for centuries. It has been assumed that is due to the fact that diabetic patients have a compromised ability to respond to infectious challenges which predisposes the patient to bacterial infections such as periodontal disease.

Over the past decade, a growing body of scientific evidence suggests an exquisite association between oral infection (eg, viruses, bacteria, yeast) and systemic diseases. However, the possibility that periodontal disease either predisposes or exacerbates the diabetic condition has received only little attention. This review highlights the two-way relationship between diabetes mellitus and periodontal disease.

Key words: Diabetes mellitus, periodontitis. AGE

Introduction

Periodontitis has been defined as an inflammatory disease of supporting structures of teeth, of specific bacterial origin which progress with episodic attachment loss. The destructive process of periodontitis is thought to begin with the accumulation of biofilms. Continued destruction is thought to occur as a result of the host inflammatory response against these bacteria and from release of toxic products from the pathogenic plaque[1].

Diabetes mellitus is a disease of metabolic disregulation which develops from either a deficiency in insulin production (IDDM) or impaired insulin utilization (NIDDM).[1] Diabetes mellitus includes a number of diseases resulting from the malfunction of insulin dependent glucose homeostasis. Classically diabetes presents with symptoms. Which include polyphagia, polydypsia and polyuria. These are symptoms, which are a direct result of hyperglycemia and resultant osmotic imbalance[2,3].

Both diabetes mellitus and periodontitis are chronic diseases affecting large number of population worldwide[3]. A relationship between periodontal disease and diabetes mellitus has been established and it is clear that diabetic control is important in the management of periodontal diseases. It also appears that periodontal infections may adversely affect the metabolic control and treatment of periodontal disease appears to result in better metabolic control of type 2 diabetes.

The 5 major complications of diabetes include[4].

- Retinopathy
- Nephropathy
- Neuropathy
- Macro vascular disease.
- Altered wound healing.

The sixth complication has been recognized as periodontitis (Loe et al 1992).

Pathogenesis:

Two possible mechanisms have been proposed for their abnormalities.

1. The polyol pathway where glucose is reduced to sorbitol by the enzyme aldol reductase. Sorbitol is considered a tissue toxin and has been implicated in most of the complication of diabetes.
2. Production of advanced glycation end products (AGEs) due to non-enzymatic additions of hexoses to proteins. This alteration of many of the body proteins alter, which includes collagen, hemoglobin, plasma albumin, lens protein, and lipoprotein, alters their functions[3,5].

Two distinct pathways have been suggested in the association of diabetes mellitus and periodontitis.

1. A direct casual relationship in which the consequences of diabetes act as modifiers of periodontal diseases expression[6].
2. A common pathological defect which results in a host susceptible to either, or both diseases.

Strong support for the hypothesis that the activation of RAGE contributes to the pathogenesis of periodontitis in diabetes has recently been provided in streptozotoxin-induced diabetic mice. When these animals were infected with P.gingivalis, the resultant alveolar bone loss was diminished in a dose-dependent fashion by treatment with soluble RAGE[7].

Effects of AGEs on Periodontium[2]:

People with diabetes, especially those with poor glycemic control, accumulate high levels of irreversibly glycated proteins called advanced glycation end products (AGEs) in the tissues, including the periodontium. AGEs are a primary link between numerous diabetic complications, because they induce marked changes in cells and extra cellular matrix components. These changes, including abnormal endothelial cell function, capillary growth and vessel proliferation, also occur in the periodontium of same people with diabetes.

The accumulation of AGEs in patients with diabetes also increases the intensity of immuno-inflammatory response to periodontal pathogens, because inflammatory cells such as monocytes and macrophages have receptor for AGEs. Interactions between AGEs and their receptors on inflammatory cells result in the increased production of proinflamatory cytokines such as IL-1ß and TNF-α. This interactions may be the cause of the marked elevation in GCF levels of IL-Iß and TNF-α seen in subjects with diabetes compared with those without diabetes, and it may contribute to the increased prevalence and severity of periodontal disease found in people with diabetes[2,8].

The effects of periodontal disease on diabetes[4]:

The mechanism by which periodontal disease may affect the diabetic state have been elucidated only recently. Both periodontal disease and diabetes, especially type 2 diabetes, have major inflammatory components. Chronic periodontal diseases also have the potential to exacerbate insulin resistance and worsen glycaemic control, while periodontal treatment that decreases inflammation may help diminish insulin resistance[4,9].

Patience with inflammatory periodontal diseases often have elevated serum levels of proinflammatory cytokines. These levels are exacerbated in diabetics. This has the potential to increase insulin resistance and make it more difficult for the patient to control his or her diabetes[10]. Research shows improvement in glycaemic control after periodontal therapy in diabetic patients[4]. In a recent study of subjects with type 2 diabetes and periodontitis, Iwamato and colleagues found that periodontal treatment to have a significant correlation with reduction in serum levels of TNF-α[11]. This reduction in TNF-α levels was accompanied by a significant reduction in mean HbA1c values (from 8.0 to 7.1%). This suggests that a reduction in periodontal inflammation helps decrease inflammatory mediators in the serum that are associated with insulin resistance, thereby improving glycaemic control [4].

HYPOTHESIS FOR THE ASSOCIATION BETWEEN DIABETES AND PERIODONTITIS:

Two hypotheses have been proposed in this regard.

First, which proposes a direct causal or modifying relationship in which the consequent hyperglycemia and hyperlipideima of diabetes result in metabolic alteration, which may then exacerbate the bacteria induced inflammatory periodontitis[6,7].

Second, proposes that an unfortunate combination of genes could result in a host who, under the influence of a variety of environmental stressors, could develop both periodontitis and diabetes mellitus. This view is supported by the observation of common immune mechanism involved in the pathogenesis of both diabetes and periodontitis. Their genetic association with the HLA region of chromosome 6, where a number of genes involved in the immune response are situated, and the bi-directional association indicating that, not only is the prevalence of periodontitis higher in diabetics than non-diabetics, but also that prevalence of diabetes is higher in persons with periodontitis[12].

Several studies revealed that the degree of glycemic control is an important variable in relationship between diabetes and periodontitis. A large scale analysis showed that individuals with type 1 diabetes manifested advanced periodontal diseases with higher prevalence and severity of gingival inflammation and periodontal destruction being seen in those with a higher glycemic index. Significantly more attachment loss and alveolar bone was lost in type 1 diabetic patients who had poor glycemic control than those who were well controlled or non-diabetic patients. Similarly in a longitudinal study of 362 subjects, poorly controlled type 2 diabetic subjects showed an 11 fold increase in the risk for alveolar bone loss over a two-year period compared to non-diabetic control subjects.

The association between diabetes mellitus and periodontal disease is therefore considered to be bidirectional: diabetes as a risk factor for periodontitis

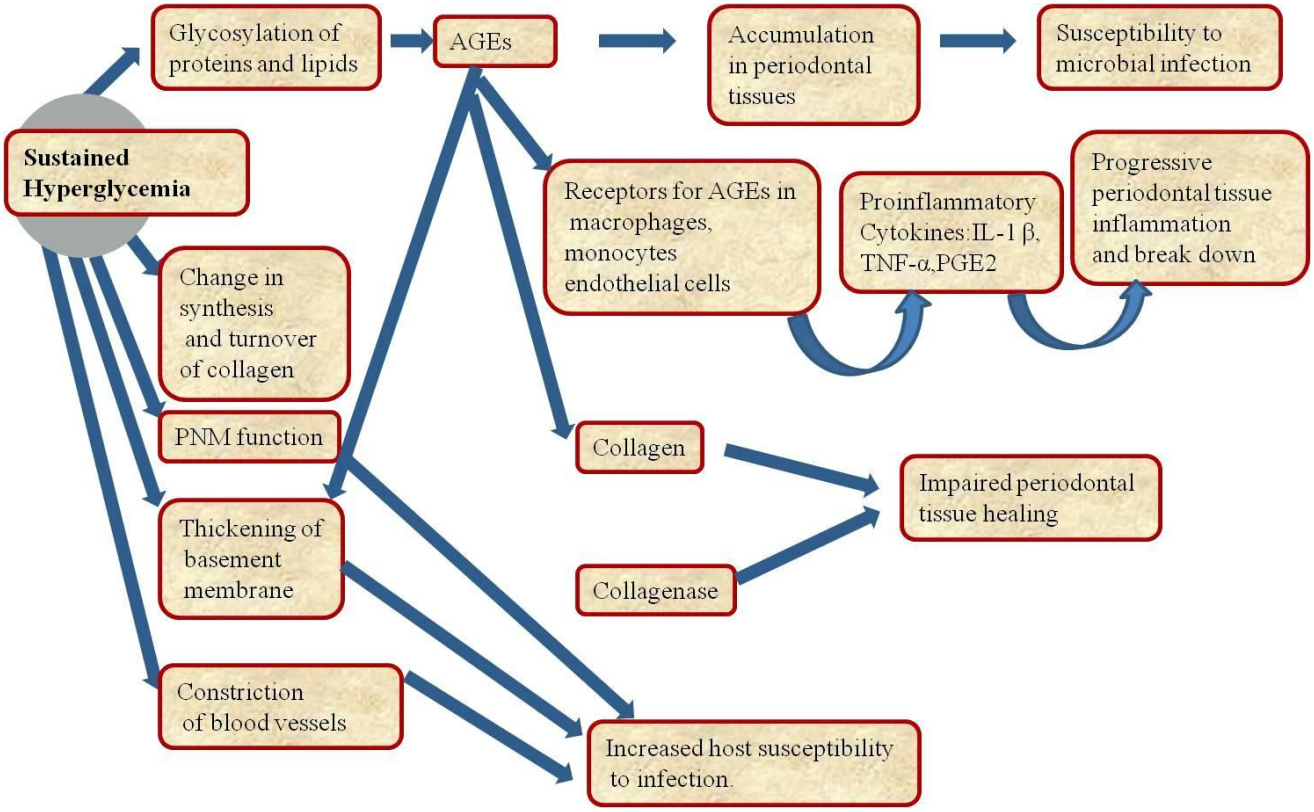

Fig 1: Mechanism by which diabetes may influence periodontal disease[1].

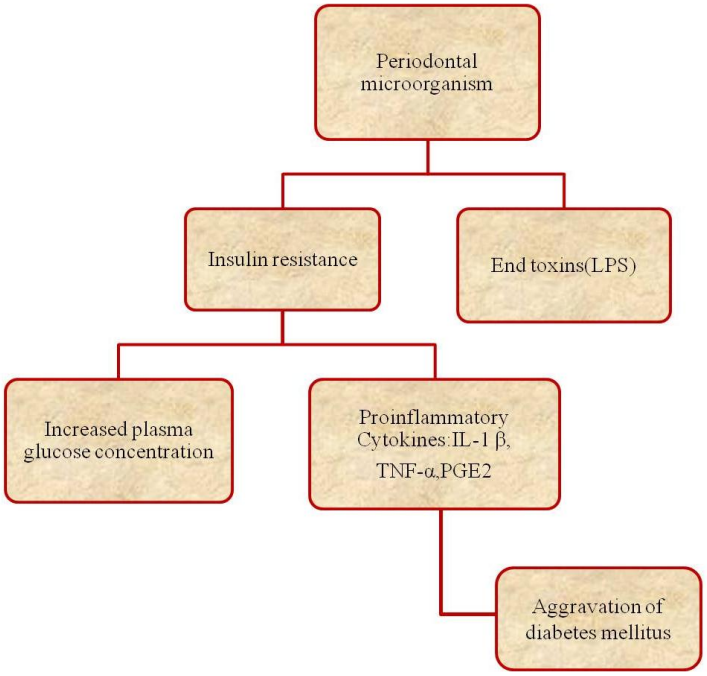

Fig 2: Mechanism by which periodontitis may influence diabetes mellitus[1].

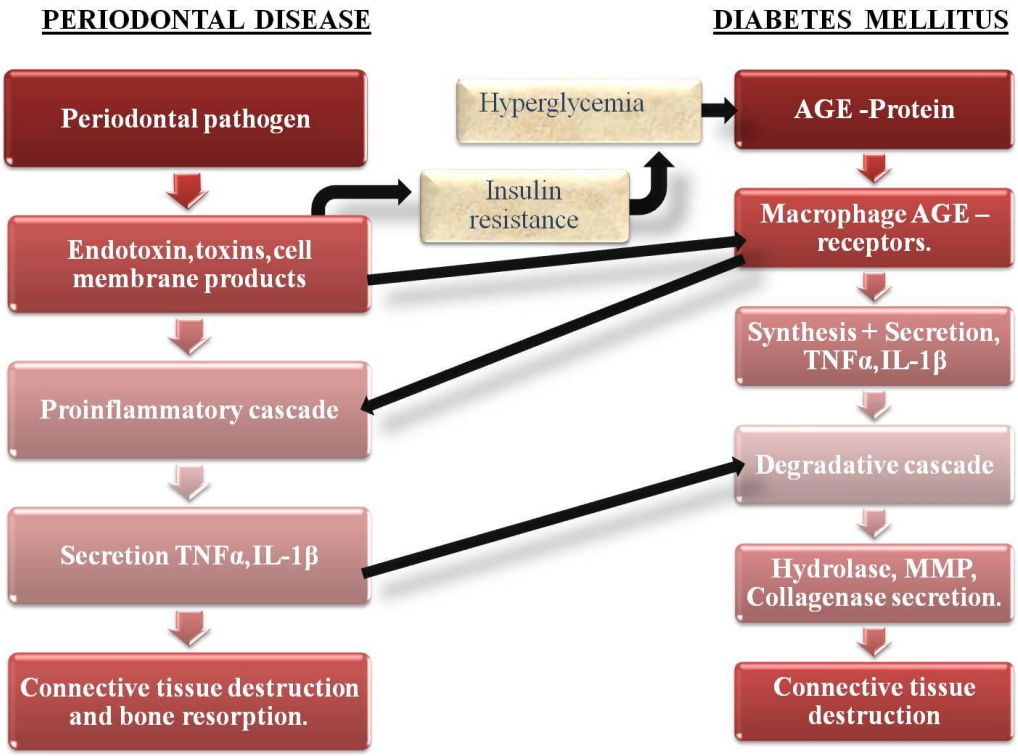

Fig 3: Proposed model for 2 – way relationship between periodontal disease and diabetes mellitus [13]

and periodontitis as a possible severity factor for diabetes. In fact periodontitis is recognized as the sixth serious complication of diabetes.

Hyperglycemia results in imbalance in lipid metabolism generally characterized by the increase in low density lipoproteins and triglycerides and fatty acids in diabetic patients. Changes in lipid metabolism are correlated with impaired functions of monocytes and/ or macrophages in successive in vitro and in vivo studies ultimately leading to the overproduction of inflammatory cytokines. Along with inflammatory cytokines (TNF alpha, IL-1β, IL-6), C-reactive protein levels are also found to be raised in periodontal patients with diabetes mellitus.

Bi directional relationship model[4]:

Diabetes is a risk factor for severe periodontal disease. Severe periodontal disease often coexists with severe diabetes mellitus. A model is presented where by severe periodontal disease increases the severity of diabetes mellitus and complicates metabolic control. It was proposed that an infection-mediated upregulation cycle of cytokine synthesis and secretion by chronic stimulus from lipopolysaccaride (LPS) and products of periodontopathic organisms may amplify the magnitude of the advanced glycation end products (AGE)-mediated cytokine response operative in diabetes mellitus. In this model, the complication of these 2 pathways, infection and AGE mediated cytokine upregulation, helps explain the increase in tissue destruction seen in diabetic periodontitis. It shows how periodontal infection may complicate the severity of diabetes and the degree of metabolic control, resulting in a 2-way relationship between diabetes mellitus and periodontal disease/infection. This proposed dual pathway of tissue destruction suggests that control of chronic periodontal infection is essential for achieving long-term control of diabetes mellitus[4].

Key points[11]:

	People with poorly controlled diabetes (both type 1 and type 2 diabetes mellitus, both adults and children) must be considered at risk for periodontitis, and people with diabetes should be informed of this risk.
	Early diagnosis and prevention are of fundamental importance to avoid the largely irreversible tissue loss that occurs in periodontitis, and early referral of adults and children with poorly controlled diabetes to dental clinicians is indicated for periodontal screening.
	Periodontal therapy in patients with diabetes is associated with improvements in glycaemic control (HbA_{1c} reductions of approximately o.4%) that may be clinically relevant in the management of diabetes.
	Oral health should be promoted in people with diabetes as an integral component of their overall diabetes management.
	Closer collaborations between medical and dental clinical teams is necessary for the joint management of peoples with diabetes and periodontitis, and contact with dentist is important after the diagnosis of diabetes.

CONCLUSION

Both diabetes mellitus and periodontitis are chronic diseases affecting large number of population world wide. The interrelationship between the periodontitis and diabetes suggests the predisposition of systemic disease to oral infection and vice versa.

People with diabetes are more likely to have periodontal disease than people without diabetes, probably because diabetics are more susceptible to contracting infections. In fact, periodontal disease is often considered the sixth complication of diabetes.

Researches suggests that the relationship between periodontal diseases and diabetes goes both ways- periodontal disease may make it more difficult for people who have diabetes to control their blood sugar.

Severe periodontal disease can increase blood sugar, contributing to increased periods of time when the body functions with a high blood sugar. This puts diabetics at increased risk for diabetic complications. Thus, diabetics who have periodontal disease should be treated to eliminate the periodontal infection. It is the duty of periodontist to educate both patient and physician about interrelationship between periodontal health and glycemic control with emphasis on inflammatory nature of periodontal disease and potential systemic effects of periodontal infection.

Dentistry has an urgent need for new information to enable the profession to identify who needs treatment and how to treat these individuals. Reducing the systemic risk associated with periodontitis requires new diagnostic tools and a set of clinical guidelines for treatment. In essence, a standard of care needs to be created.

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