REVIEW ARTICLE

Diabetes and Its Association With Periodontal Tissues

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ABSTRACT

Diabetes mellitus is a clinically and genetically heterogeneous group of disorders affecting the metabolism of carbohydrates, lipids and proteins. The prevalence of diabetes is rapidly rising all over the world at an alarming rate. Therefore, its clinical implications are increasingly assuming significant proportions. Diabetes has traditionally been linked with several disorders and complications, periodontitis being one of the many. The interrelationship between diabetes and periodontitis is long standing and the clinical evidence in favour of the same is overwhelming. Current literature supports a two way relationship between the periodontal disease and the levels of glycemic controls and in turn the overall health of the individual. This article is aimed to highlight the strength of association and the mechanism by which the two common chronic diseases i.e. diabetes and periodontitis are interlinked together. The data so far existing in this respect are confounded by varying definitions of diabetes and periodontitis and different clinical criteria's applied to define prevalence, extent, severity of periodontal disease, levels of glycemic control and complications associated with diabetes. This review is intended to help dental professionals in diagnosis and management of patients with diabetes mellitus, provide overview of relevant factors in diabetic patients to understand the pathogenesis of periodontal disease in these subjects and also to help dental and medical practitioners in getting aware as well as updated of the implications of this crucial relationship and managing their patients accordingly.

Keywords: Diabetes mellitus, Oral health, Periodontitis

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INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to defective secretion or activity of insulin.[1] Diabetes mellitus (DM) is classified into 2 clinical entities based on etiology: Type I Diabetes (T1D) and Type II Diabetes (T2D). T1D can develop at any age, but usually the onset occurs before the age of 20 years. This may result from the destruction of the insulin producing pancreatic β- cells which may involve an autoimmune or a virally mediated destructive process. Since these patients are subject to exogenous insulin supplementation therapy, they have frequent iatrogenic episodes of diabetic complication, not only due to hyperglycemia but also to hypoglycemia. T2D results either from defects in insulin molecule or from altered cell receptors for insulin and manifests as insulin resistance rather than insulin deficiency.[2]

American Diabetes Association[3] has established criteria for the diagnosis of diabetes, involving the use of either fasting blood glucose levels or two hour postprandial levels or oral glucose tolerance tests. Since single abnormal lab test is not sufficient to establish a diagnosis, any positive value must be confirmed on different day. The following criteria were to be considered under the same-

1. Pathognomonic symptoms like polyuria, polydipsia, unexplained weight loss along with casual/random plasma glucose concentration ≥ 200 mg/dl (≥11.1 mmol/l)
2. Fasting (no caloric intake for 8 hours) plasma glucose ≥ 126 mg/dl (≥7.0 mmol/l).
3. Two hour post load glucose ≥ 200 mg/dl (≥11.1 mmol/l) following an oral glucose tolerance test using a glucose load equivalent to 75 mg of anhydrous glucose dissolved in water.

In an established case of diabetes HbA1c (glycosylated haemoglobin) is used to monitor the overall glycemic control. However, the point worth mentioning here remains that glycosylated hemoglobin is continuously being formed in the erythrocytes as a direct consequence of the non-enzymatic reaction between glucose and hemoglobin and the resultant bond being highly stable one glycates the hemoglobin for the remainder of the life span of the erythrocytes i.e. approximately 123+/-23 days. Higher average blood glucose levels reflected in consequentially higher HbA1c levels (normal HbA1c levels < 6 %) are indicative of poor glycemic control.[5]
Classic complications of diabetes include retinopathy, nephropathy, neuropathy, cardiovascular disease and impaired wound healing. Periodontal disease is considered as the sixth greatest complication of diabetes.[6]
Type 1 diabetes mellitus is due to destruction of pancreatic beta cell in the islets of Langerhans of the pancreas, resulting in imbalance of the blood sugar levels. The onset of this disease is abrupt, and patients are more prone to ketoacidosis. Signs and symptoms are: polydipsia (excessive thirst), polyuria (excessive urine output) and polyphagia (excessive appetite), also weakness and fatigue.

Type 2 diabetes mellitus causes ranges from insulin resistance with relative insulin deficiency to a predominantly secretory defect accompanied by insulin resistance. Onset is gradual and is often associated with obesity. Risk factors associated with this are lack of physical activity, hypertension, increasing age dyslipidemia and genetic predilection. Another form of DM is gestational diabetes mellitus (GDM) which is glucose intolerance occurring during pregnancy.

INFLUENCE OF DIABETES ON PERIODONTAL TISSUES

Various available data reveals a strong evidence of relationship between periodontitis and levels of glycemic control. [8,9] Although some studies failed to demonstrate any relationship between the two,[10] majority of the studies have demonstrated and stated that the prevalence and severity of gingivitis are higher in individuals with poor glycemic controls. Many studies suggest that the presence of diabetes is often, but not always, associated with increased gingival inflammation. In addition, the level of glycemic control may play a role in the gingival response

ORAL MANIFESTATIONS OF DIABETES MELLITUS

Oral complications of DM[α]	
Long-term diabetic complication	**Oral implications**
Microvascular disease	- Xerostomia - Greater susceptibility of oral tissues to trauma - More opportunistic infections (e.g. candidiasis) - Greater accumulation of plaque - Greater risk of caries - Delayed wound healing - Greater susceptibility to periodontal disease
Peripheral neuropathy	- Oral paresthesia, including burning mouth or tongue - Altered taste sensations

[α] Adapted from Ress[7]

to bacterial plaque in people with diabetes, this may lead to greater accumulation of plaque.[11,12,13] Existing evidences also suggest that high glycemic levels also increases the risk of periodontitis. Epidemiologic studies in diabetic adults have shown an increase in the extent and severity of periodontitis in general.[14, 15] Meta-analyses have concluded that the majority of studies demonstrated a more severe periodontal condition in diabetic adults than in adults without diabetes.[8]

Though relationship between diabetes and periodontal disease is difficult to define conclusively. Researches suggest that this association is similar to the association between glycemic controls and the classic complications of diabetes such as retinopathy and nephropathy; namely, there is significant heterogeneity in the diabetic population. Thus, although poor control of diabetes clearly increases the risk of diabetic complications, there are many poorly controlled diabetic individuals without major complications.[16] Conversely, good control of diabetes greatly decreases the risk of diabetic complications, but there are people with well-controlled diabetes who suffer major diabetic complications nonetheless. This is well supported by the body of evidences from the epidemiological studies. A classical study on Pima Indians stated that, poor glycemic control of type 2 diabetes was associated with an 11-fold increased risk of progressive bone loss compared to non-diabetic controls, whereas well-controlled diabetic subjects had no significant increase in risk.[17] Thus, the onset and progression of the periodontal disease is greatly influenced by the metabolic control of diabetes.

MECHANISM OF INFLUENCE OF DIABETES ON PERIODONTIUM

The mechanism by which poor diabetic control results in development of periodontitis is still not fully understood. Several mechanisms have been listed to explain this association. Decreased fibroblast proliferation and collagen synthesis, enhanced collagen glycosylation and cross linkage results in altered metabolism of collagen, in prolonged hyperglycemic conditions. This leads to the replacement of the normal collagen structure with a more highly cross linked and polymerized structure that has decreased degrading properties than normal collagen. This results in consequential increased removal of gingival collagen fibers due to increased collagenase activity. The result is thickening and alteration of the basement membrane of the adjacent capillaries and precapillary arterioles and vascular degeneration of the gingiva causing decreased glucose oxidation and oxygen consumption. Severe periodontal destruction and aggressive removal of connective tissue is observed owing to the above mentioned angiopathies which compromises the delivery of nutrients and removal of waste products from the aforementioned sites.[18]

Alterations in the host immune- inflammatory response may have a major influence on the increased prevalence and severity of periodontal destruction seen in diabetes. This is supported by the evidences found in many culture studies stating that the bacterial microflora at periodontally diseased sites in diabetic subjects is similar to the microflora at similarly diseased sites in non-diabetic subjects.[19,20] Few studies suggest that colonization with Gram-negative organisms such as P. gingivalis, Tannerella forsythensis, and Prevotella intermedia, have significantly higher inflammatory mediators. Their disseminating induces an elevated inflammatory state, leading increased serum inflammatory markers.[21,22,23]

Recent studies have documented that the increased severity of periodontitis seen in diabetic patients is due to increased up regulation of monocyte/ macrophages to bacterial antigens. This hyper- responsiveness resulting in enhanced production of proinflammatory cytokines like interleukines 1- β (IL-1 β), tumor necrosis factor- α (TNF- α) and prostaglandin E2.[24] These elevated serum levels of inflammatory mediators associated with diabetes are reflected in similarly increased levels of these mediators in gingival crevicular fluid.[25]

Important link between all of these changes and the subsequent development of the major complications of diabetes is the glycosylation of proteins, lipids and nucleic acids.[26] The hyperglycemia mediated formation and accumulation of these proteins are known as

Advanced Glycation End products (AGEs)[27]. AGEs are irreversibly chemically altered proteins resulting from non-enzymatic addition of hexoses by a slow and continuous process in hyperglycemic state. The process commences with the attachment of glucose to amino group of proteins resulting in the formation of an initial unstable Schiff base product which through a slow chemical rearrangement is converted to a more stable yet reversible glucose protein products known as amdori product. In the event of sustained hyperglycemia as in uncontrolled diabetes mellitus, this amdori product transforms into a highly stable configuration. The resulting carbohydrates associated stable proteins produce multiple cell to cell and cell to matrix interactions and are commonly thought to be a major link between the various diabetic complications. The site of AGE generation is periodontium and a higher level has been associated with diabetes mellitus in human subjects.[28] The AGEs have been further found to be associated with collagen protein and this association produces a highly stable cross linked collagen configuration that is especially resistant to enzymatic degradation and tissue turnover and therefore persists within the tissues.. This altered, highly stable, enzyme resistant collagen then accumulates within the walls of blood vessels producing a narrow lumen and atherosclerotic changes owing to its increased affinity for low density lipoproteins(LDLs). It also results in thickening of the basement membrane, increased production of vascular endothelial growth factor (VEGF) which is a multifunctional cytokine that induces neovascularization. AGEs may function via receptor independent mechanism or may directly interact on cell surfaces at receptor for AGEs (RAGE). Normally present at low levels in endothelial cells, smooth muscle cells, neurons and monocytes. [29] This expression is enhanced in diabetes. Thus, interaction of AGE with fibroblast RAGE results in decreased production and remodeling of collagen.[30] This decreased remodeling results in accumulation of altered collagen in the oral tissues leading to signs like xerostomia in diabetic conditions. Xerostomia further complicates the periodontal conditions as the cleansing and anti- microbial action of saliva is lost. It also makes individual more susceptible to dental caries. Accumulations of AGEs in the periodontal tissues play an important role in the pathogenesis of periodontitis. AGEs accumulates two- folds in the periodontal tissues as compared to other tissues. Increased accumulation of AGEs and their interaction with RAGE in diabetic gingiva leads to vascular dysfunction and hyperpermeability, loss of effective tissue integrity and barrier function, alteration, immobilization and activation of mononuclear phagocytes, critical mediators in generation of proinflammatory cytokines and matrix metalloproteinase's (MMP's).[30]

INFLUENCE OF PERIODONTAL INFECTION ON DIABETES

Metabolic state in diabetes can be significantly influenced by periodontal disease. Periodontal diseases may induce or perpetuate an elevated systemic chronic inflammatory state. Diabetic subjects with severe periodontitis are at six-fold increased risk of worsening of glycemic control over time compared to diabetic subjects without periodontitis.[31] Acute bacterial and viral infections are known to increase insulin resistance in people without diabetes, a condition which often persists for weeks to months after clinical recovery from the illness.[37] Systemic dissemination of periodontopathic micro-organisms causes bacteremia or endotoxemia, results in an elevated levels of inflammatory mediators and there markers like Interlukines-6 and C-reactive protein .Periodontal interventional trials have suggested a significant potential metabolic benefit of periodontal therapy in patients with diabetes.[32,37,38,39]

MECHANISM OF INFLUENCE OF PERIODONTAL INFECTION ON DIABETES

Periodontal diseases may induce or perpetuate elevated systemic chronic inflammatory state.[30] Chronic Gram-negative periodontal infections may result in increased insulin resistance and poor glycemic control as is seen in acute bacterial and viral infections. This may contribute to cycle of hyperglycemia, non-enzymatic irreversible glycation, AGEs of protein binding with further

accumulation. Monocytes from patients with diabetes produce 24 to 32 times increase level of TNF- α, when stimulated by periodontal pathogen than do monocytes from subjects without diabetes.[34] TNF- α is an antagonist to the cell surface insulin receptor substrate (IRS-1), which inhibits phosphorylation and translocation of insulin receptor.[35] Resulting inhibition of intracellular glucose transport and insulin action contributing to insulin resistance. This explains why periodontitis increases the risk of poor glycemic control in patients with type 2 diabetes[31] and may also explain why improvement in glycemic control has followed periodontal therapy.[36]

Treatment that reduces periodontal inflammation may restore insulin sensitivity, resulting in improved metabolic control.[37-40]

The line of therapy for periodontitis for patients suffering from diabetes remains the same as for high risk patients suffering from periodontitis. The categories of patients that may be regarded as highly predisposed towards developing diabetes and hence periodontitis are as those with a family history of diabetes, dyslipidemia, previous gestational diabetes, hirsutism, obesity and smoking. Therefore the diabetic patients must mandatorily undergo regular screening to detect the onset and intervene promptly at very first signs of disease activity.

CONCLUSION

Diabetes has an impact on all the tissues of the body and oral tissues are not an exception to it. The puzzle of relationship between periodontal tissues and diabetes is typical to be solved, because of the multi factorial, complex aetiopathogenesis of both disease entities. But researches so far conducted in this regard have indicated that diabetes increases the risk of periodontitis and vice versa. Though the exact mechanism is not clear but the alteration in the host defenses and normal tissue homeostasis appear to play a major role. Studies establishing the link of periodontal infection and periodontal treatment on the glycemic levels have concluded a strong positive association between the two. Still further researches in this regard are needed to delineate more precisely the pathway through which the two influence each other.

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