

Periodontal Disease and Diabetes - A Two Way Street Dual Highway?

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Abstract:

Periodontitis is considered to be the sixth most common complication of diabetes. There is a two way relationship in which periodontal disease has adverse impact on glycemic control and in turn diabetes exaggerates periodontal infection, affecting the overall general health of an individual. In this article we have tried to review the recent research developments and mechanisms by which both diabetes and periodontal disease cause mutual destruction. Our aim of this article is to make aware, both general dental and medical practitioner about interrelationship between periodontal disease and diabetes with special emphasis on importance of mutual consultation between the two fraternity, which in turn significantly contributes to general well being of an individual.

Key Words: Diabetes, Periodontitis, Amadori Product, AGE's.

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 which contain significant bacterial masses on the tooth surface at or below the gingival margin (Gibbons & Van-Houte, 1980). 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.

Studies conducted by National Center for Health Statistics & National Institute of Dental and Craniofacial Research have spurred researchers in the dental community to investigate the possibility of risk factors other than bacterial plaque which would exacerbate and perpetuate the progression of periodontal disease (Miller et al, 1987; Brown & Loe, 1993). There is at present a rapidly increasing evidence which has implicated a variety of systemic diseases such as diabetes, HIV, inherited chromosomal disorders, environmental factors, behavioral influences and osteoporosis as playing important roles in development and progression of periodontal disease. There is a strong relationship between periodontal health or disease and systemic health or disease. This means a two way relationship in which periodontal

disease in an individual may have powerful influence on individual's systemic health or disease as well as most customary understood role that systemic disease may have an influence on individual's periodontal health or disease (Dumitrescu & Inagaki, 2010).

Diabetes Mellitus:

Diabetes mellitus is a disease of metabolic disregulation, which develops from either a deficiency in insulin production (IDDM) or impaired insulin utilization (NIDDM). It is characterized by the classic triad of symptoms like polyuria, polydipsia and polyphagia.

Insulin dependent diabetes mellitus (IDDM) results from the destruction of the insulin producing β cells of the pancreas which may involve an autoimmune or a virally mediated destructive process. Non insulin dependent diabetes mellitus (NIDDM) results either from defects in insulin molecule or from altered cell receptors for insulin and manifests as insulin resistance rather than insulin deficiency (Szopa et al, 1993; Atkinson & Maclaren, 1990; Current Concepts, 1999).

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 (Loe, 1993).

The diagnosis of diabetes is based on criteria established by American Diabetes Association -2005 and involves the use of either fasting blood glucose levels or two hour postprandial levels or oral glucose

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tolerance tests. Since single abnormal lab test is not sufficient to establish a diagnosis, any positive value must be confirmed on different day: 1) Symptoms of diabetes like polyuria, polydipsia, unexplained weight loss, and Casual (any time after last meal) plasma concentration of ≥ 200 mg/dl. 2) Fasting (no caloric intake for 8 hours) plasma glucose ≥ 126 mg/dl. 3) Two hour post load glucose ≥ 200 mg/dl during an oral glucose tolerance test. The test is performed using a glucose load containing the equivalent of 75gm anhydrous glucose dissolved in water. The normal fasting plasma glucose level is < 100 mg/dl. Impaired fasting glucose is diagnosed when fasting plasma level of glucose is ≥ 100 mg/dl but ≤ 125 mg/dl. Normal post load glucose is < 140 mg/dl. Impaired glucose tolerance is diagnosed when 2 hour post load plasma glucose is ≥ 140 mg/dl but ≤ 199 mg/dl. (Mealey & Oates, 2006).

Oral manifestations of diabetes mellitus:

There is evidence demonstrating that some of the commonly occurring signs and symptoms of diabetes occur in oral cavity. Depending on the age of the patient, duration of disease, and control or management of disease, the oral manifestations can vary from normal to severe.

Uncontrolled diabetes:

- Chelosis and tendency towards drying and cracking.
- Burning sensation in mouth or tongue due to xerostomia or candidiasis.
- Decrease in salivary flow, leading to increased caries rate.
- Oral mucosa is red, edematous and ulcerated
- Most striking changes are the reduction in defense mechanisms and increased susceptibility to infections leading to destructive periodontal disease.

Controlled diabetes:

In well controlled diabetes none of the previously mentioned changes are found. Accumulating data regarding the effect of diabetes on oral cavity suggest that oral tissues are adversely affected by uncontrolled diabetes similar to other body systems and increased susceptibility to oral infections including gingivitis, periodontitis and delayed wound healing (Mealey, 1999).

Diabetes and Periodontal Disease:

Periodontitis in IDDM starts to appear after the age of 12 years, with higher prevalence in older individuals, whereas in NIDDM patients have higher prevalence irrespective of their age. Patients showing overt diabetes over a period of more than 10 years have greater loss of periodontal structures, than those with a diabetic history of less than 10 year (Papapanou, 1996).

Periodontal disease is most consistent finding in poorly controlled diabetic patients. Approximately 75% of these patients have periodontal disease with increased alveolar bone resorption and inflammatory gingival changes. Diabetics, whose diabetes is under good control are also found to have a higher incidence and greater severity of periodontal disease.

Individuals with poorly controlled diabetes present with increased gingival bleeding, enlarged gingiva, sessile or pedunculated gingival polyps, increased probing depths, increased attachment loss, increased tooth loss, increased alveolar bone loss and tendency towards abscess formation (Mariotti, 1999). Periodontal disease is more frequent and severe in diabetic individuals with more advanced systemic complications, which does not correlate with increased levels of plaque and calculus (Bacić et al, 1988).

The mechanism by which diabetes mellitus contributes to development of periodontitis remains unclear although several mechanisms have been proposed. Prolonged exposure to hyperglycemic condition results in decreased fibroblast proliferation, decreased collagen synthesis, enhanced collagen glycosylation and cross linkage resulting in defective collagen metabolism and normal collagen is replaced with highly polymerized and cross linked collagen. Increased collagenase activity results in excess removal of gingival collagen fibers. Vascular basement membrane thickening and alteration, narrowing of the lumina of the capillaries and precapillary arterioles and vascular degeneration of the gingiva leading to reduced oxygen consumption and oxidation of glucose. These angiopathies contribute to compromised delivery of nutrients to the surrounding tissues and poor elimination of waste products necessary for maintenance of gingival tissues (Krejci & Bissada, 2000). All the above mentioned mechanisms contribute to aggressive removal of connective tissue and severe periodontal destruction.

It has been recently demonstrated that in diabetics, an upregulated proinflammatory monocyte

response results in enhanced production of cytokines, like tumor necrosis factor- α (TNF- α) interleukin 1- β (IL 1 β) and prostaglandin E₂, which is linked to increased severity of periodontal disease. These factors strongly suggest that, in diabetes a number of abnormal host effector mechanisms converge to lead to a range of complications (Grant-Theule, 1996).

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 (Vlassara, 1994; Brownlee, 1994). The hyperglycemia mediated formation and accumulation of these proteins are known as (AGEs) Advanced Glycation End products (Brownlee, 1994; Brownlee & Cerami, 1981). AGEs are chemically irreversible proteins which have been altered by the non enzymatic addition of hexoses and form slowly and continuously in hyperglycemic condition (Brownlee, 1992). Formation of AGEs begins with the attachment of glucose to amino groups of proteins to form an unstable Schiff base products. Through a slow chemical rearrangement, these are converted to a more stable but still reversible glucose protein products known as Amadori product. Normalization of hyperglycemia at this stage results in reversible Amadori product. If hyperglycemia is sustained the Amadori product becomes highly stable and form AGEs which are irreversible. Thus even if hyperglycemia is corrected, the level of AGEs in the affected tissues does not return to normal (Vlassara, 1994; Brownlee, 1994; Monnier et al, 1996). AGEs form and accumulate in number of circumstances such as ageing, renal failure and uncontrolled diabetes. Accumulation of AGEs in the tissue may result in significant alteration of normal cellular composition and structure. With the alteration of many body proteins such as collagen, hemoglobin, plasma albumin, lens proteins and lipoproteins, come an alteration in their respective functions. In addition to apparently receptor independent mechanisms, AGEs may directly interact on cell surfaces at receptor for AGEs (RAGE), a member of immunoglobulin super family of cell surface molecules. In normal individuals RAGE is present at low levels in a number of cell types including endothelial cells, smooth muscle cells, neurons and monocytes (Schmidt et al, 1994 & 1996; Vlassara & Bucala, 1996). However, in perturbed states, such as diabetes, the expression of RAGE on critical cell is strikingly enhanced. The interaction of AGEs with monocyte RAGE results in increased cellular oxidant

stress that leads to enhanced chemotaxis and activation of monocytes with resultant release of four times more of pro inflammatory cytokines IL- 1, and twenty four to thirty two times of TNF- α compared to normal individuals (Schmidt et al, 1994 & 1996; Kirsstein et al, 1992; Vlassara et al, 1988). Interaction of AGE with fibroblast RAGE results in decreased production and remodeling of collagen (Lalla et al, 2000).

Effects of AGEs on Periodontium:

AGEs accumulate twofold in human diabetic periodontium as compared to other tissues. This accumulation plays an important role in the pathogenesis of diabetes associated periodontitis. 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) (Lalla et al, 2000). Grossi and Genco have postulated that, if glucose mediated AGE accumulation altered the migration and phagocytic activity of mononuclear and polynuclear cells, a more pathogenic sub gingival flora would result (Grossi & Genco, 1988). With maturation and transformation, the subgingival flora would become more Gram -ve and in turn produce a source of chronic systemic challenge through the ulcerated pocket epithelium. This chronic infection further trigger cytokine upregulation especially TNF- α and IL-1 leading to further connective tissue degradation and destruction.

Influence of Periodontal Infection on Diabetes:

Studies have shown that diabetic patients with periodontal infection have a greater risk of worsening glycemic control overtime compared to diabetic subjects without periodontal disease (Taylor et al, 1996). Periodontal interventional trials have suggested a significant potential metabolic benefit of periodontal therapy in patients with diabetes (Mealey & Ocampo, 2007). Several studies of diabetic subjects with periodontitis have shown improvements in glycemic control following scaling and root planing combined with adjunctive systemic doxycycline therapy. The magnitude of change is often about 0.9 to 1.0% in HbA_{1c} test (glycosylated hemoglobin) (Miller et al, 1992; Grossi et al, 1997). Studies have shown that systemic infections such as viral or bacterial infections

increase insulin resistance and have adverse impact on glycemic control (Yki-Järvinen et al, 1989; Sammalkorpi, 1989). Recent evidence suggest that chronic infections like periodontitis may induce a chronic state of insulin resistance which would then result in poor glycemic control which would contribute to the cycle of hyperglycemia, non enzymatic irreversible glycation, AGEs of protein binding with further accumulation (Nishimura & Murayama, 2001; Mealey & Oates, 2006). Blood levels of TNF- α , IL-6 and C-reactive proteins (pro inflammatory cytokines) are increased in patients with diabetes especially in those with periodontal disease (Noack et al, 2001). 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 (Salvi et al, 1997). TNF α is an antagonist to the cell surface insulin receptor substrate (IRS-1), which inhibits phosphorylation and translocation of insulin receptor (Ling et al, 1994). 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 (Taylor et al, 1996), and may also explain why improvement in glycemic control has followed periodontal therapy in studies of diabetic subjects (Miller et al, 1992; Stewart et al, 2001). Thus periodontal treatment may reduce inflammation locally and also decrease serum levels of the inflammatory mediators that may cause decreased insulin resistance thereby positively affecting glycemic control (Iwamoto et al, 2001). Thus relation between periodontal disease and diabetes may be a two way street, a dual highway of catabolic response and tissue destruction resulting in more severe periodontal disease and less glycemic control (Fig. I). Various mechanisms of diabetic influence on periodontium explained in Fig. II.

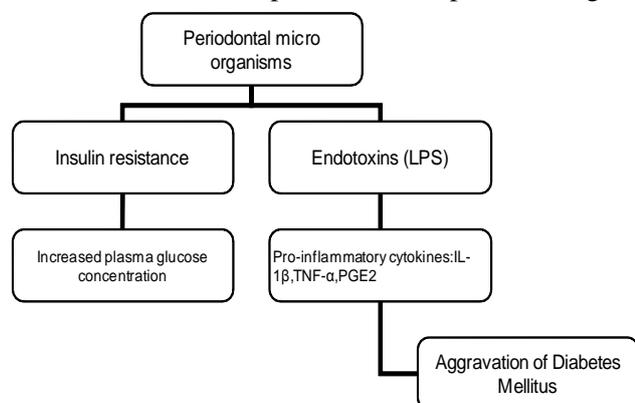


Fig. I: Mechanisms by which periodontitis may influence diabetes mellitus

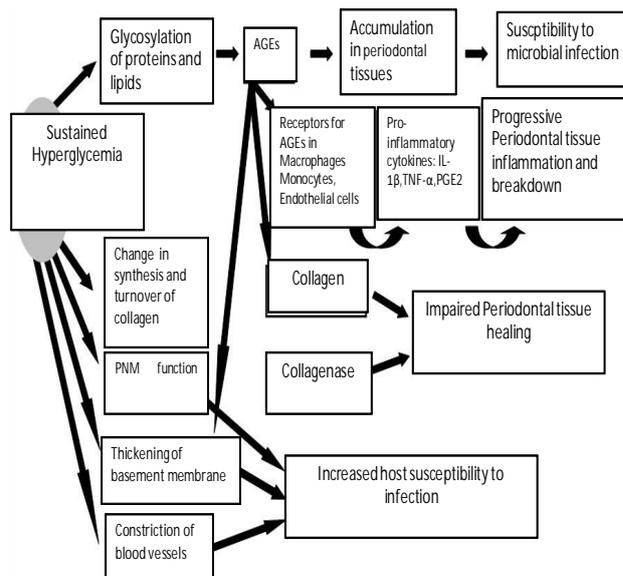


Fig. II: Mechanisms by which diabetes may influence periodontal disease.

Table I: Periodontal maintenance for well controlled diabetes.

Patient characteristics	Periodontal maintenance	Frequency
Healthy periodontium; no or minimal localized gingivitis	Record probing depths and bleeding score; deplaque	Annually
Healthy periodontium, generalized gingivitis	Record probing depths and bleeding score; deplaque, OHI	Annually
Chronic, mild to moderate periodontal disease	Record probing depths and bleeding score; deplaque, OHI	3 to 4 months
Advanced attachment loss	Referto periodontist, monitor, record probing depths & bleeding score, deplaque, OHI	3 to 4 months

Table II: periodontal maintenance for poorly controlled diabetes.

Patient characteristics	Periodontal maintenance	Frequency
Healthy periodontium; no or minimal localized gingivitis	Record probing depths and bleeding score; deplaque, OHI	Every 6 months
Healthy periodontium, generalized gingivitis	Record probing depths and bleeding score; deplaque, OHI	Every 4 to 6 months
Chronic mild to moderate periodontitis	Refer to periodontist, monitor, record probing depths & bleeding score, deplaque, OHI	Every 4 to 6 months
Advanced or aggressive periodontitis	Refer to periodontist, monitor, record probing depths & bleeding score, deplaque, OHI	Every 3 months

Diabetes and Gingival Crevicular Fluid (GCF) Glucose Levels:

Increased blood glucose results in increased levels of gingival crevicular fluid (GCF) glucose. Invitro studies have shown decreased chemotaxis of

periodontal ligament fibroblasts to platelet derived growth factor when placed in hyperglycemic environment (Nishimura et al, 1998). Thus elevated GCF glucose levels adversely affect periodontal wound healing.

Periodontal Vasculature:

Changes affecting renal, retinal vasculature, also affect periodontium in diabetes. Increase in thickening of gingival capillary endothelial cell basement membrane and wall of small blood vessels takes place. This impairs oxygen diffusion and nutrition provision across basement membrane which alters normal tissue homeostasis leading to increased severity and progression of periodontal disease (Frantzis et al, 1971; Listgarten et al, 1974; Seppälä et al, 1997).

Collagen Metabolism:

Increased collagen breakdown through stimulation of collagenase activity has been observed in periodontium of diabetic individuals. Collagenase primarily degrades more newly formed and therefore more soluble collagen macromolecules. Sustained hyperglycemia results in AGE modification of existing collagen with increased cross linking. This results in rapid degradation of recently synthesized collagen by host collagenase and predominance of older highly cross linked modified collagen. Since collagen production and degradation exist as a highly balanced homeostatic mechanism, change in collagen metabolism result in altered wound healing. Impaired wound healing is a well recognized complication of diabetes and may affect any tissues including periodontium (Ramamurthy & Golub, 1983).

The cytokines also effect the increased production of MMPs by major cell types of periodontium. MMPs are responsible for increased bone resorption and connective tissue breakdown (Ryan et al, 1996).

Management:

The goal of diabetes control should be aimed at glycemic control regulation as evidenced by diabetes control and complications trial (DCCT, 1986), in which through intensive insulin therapy, the risks of development and/or progression of existing retinopathy, nephropathy, neuropathy and severity of periodontal disease were reduced significantly. The American diabetes association recommends vigorous glycemic control for patients in the NIDDM category as well.

The initial dental therapy for patients with diabetes mellitus as with all patients should be directed towards control of all acute oral infections, at the same time, communication may be established with the patients physician so that a plan can be developed to obtain control of blood glucose levels. It is important to advise the physician of the periodontal status, since the presence of infections, including advanced periodontitis may increase insulin resistance, and contribute to worsening of diabetic state. Several studies have shown that control of periodontal infection through mechanical therapy combined with systemic antibiotics improve glycemic control leading to reduced requirement of insulin in insulin dependent diabetes mellitus patients (Stewart et al, 2001; Darré et al, 2008; Madden et al, 2008). As above studies have demonstrated that control of periodontal disease can enhance glycemic control, it would seem logical to include periodontal disease control as an integral part of diabetes management. It is also necessary to study what type of periodontal therapy, like mechanical debridement, surgical or local drug delivery reduces circulating AGEs and TNF α levels and whether blocking of TNF α with neutralizing antibodies is effective in improving insulin resistance without conventional periodontal therapy (Tan et al, 2006).

Guidelines for Dentist and Periodontist:

Prevention and control of periodontal disease must be considered as an integral part of diabetes control. The principles of treatment of periodontitis in diabetic patients are the same as those for non diabetic patients. Major efforts should be directed at preventing periodontitis in patients who are at risk of diabetes. Diabetic patients with poor metabolic control should be seen more frequently especially, if periodontal disease is already present. Periodontist should understand the diagnostic and therapeutic modalities used in diabetes care. They should thoroughly understand the pharmacologic agents commonly used to treat diabetes and the risk, they pose in the form of hypoglycemia and its treatment in dental clinic is a must. 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 (Table I & II; Matthews, 2002).

Summary:

Ensuring oral health in patients with diabetes requires an expanded scope of medical and dental knowledge. There is undoubtedly a close relationship exists between diabetes and periodontal disease, a relationship requiring further study and exploration. Diabetes increases the risk of periodontal destruction, especially in patients having poor glycemic control. These patients are most likely to report to dental office with significant periodontal treatment needs. All diabetic patients should have routine periodontal evaluation and preventive therapy. The practitioner, who understands the role of diabetes in etiology of oral diseases, the potential for oral infections to influence glycemic control, the current medical therapeutic approaches to diabetes and implications of diabetes on dental care provides patient with the best chances of successful treatment outcomes.

As health care professionals, we need to be more cognizant of interrelationship between diabetes and periodontal disease. The time has come for all medical and dental practitioners to practice at a heightened level of awareness regarding interrelationship between diabetes mellitus and periodontal disease. The best treatment protocol includes referral of patients to respective specialists like diabetologist and periodontist for specific treatment concerns.

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