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Review Article

DIABETES AND PERIODONTIUM- A BIDIRECTIONAL LINK: A REVIEW

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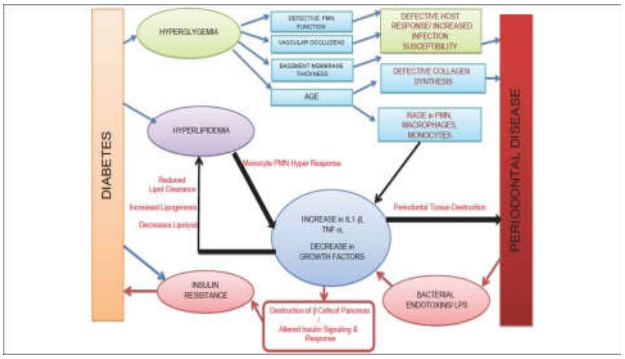
ABSTRACT

Health sciences are in the midst of major transition. The oral cavity contains almost half the commensal bacteria in the human body, approximately six billion microbes. The oral cavity is remarkably dynamic and continuously challenged by opportunistic infection on one hand and the oral complications of systemic diseases on the other. Periodontitis is an oral disease with documented risk factors including smoking, specific plaque bacteria, diabetes mellitus, hypertension, etc. While this link between systemic disease and periodontitis was thought to be unidirectional, mounting evidence in the last decade suggests that the relationship may be bi-directional. Therefore, oral health is an important component of general health and individuals with periodontitis may be at risk for other diseases as well. The association between diabetes and periodontal diseases has long been discussed with conflicting conclusions. The present paper discusses the bidirectional relationship between periodontitis and diabetes mellitus.

INTRODUCTION

Investing and supporting tissues of the teeth are called Periodontium which includes: gingiva, alveolar bone, periodontal ligament and cementum. Diabetes mellitus is caused by the malfunction of insulin dependent glucose and lipid metabolism, and presents with the classical triad of symptoms: polydypsia, polyuria and polyphagia which are often accompanied by chronic fatigue and weight loss. Complication, include retinopathy, nephropathy, neuropathy and cardiovascular disease. The association between diabetes and periodontal diseases has long been discussed with conflicting conclusions. Both the diseases have a high incidence in the general population as well as a number of common pathways in their pathogenesis. (Soskolne WA and Klinger A, 2001)

Historically, research concerning the relationship between diabetes and periodontitis focused on vascular changes in the periodontal tissues, granulocyte hypofunction and increased tissue liability resulting from reduced collagen production, enhanced gingival collagenase activity and changes in oral microflora.



Diabetes Induced Systemic Inflammatory State

Salvi GE, Collins JC,1997 showed that circulating monocytes from diabetic patients exhibit an exaggerated inflammatory response to gram negative bacterial lipopolysaccharides (LPS) and released large amounts of inflammatory mediators and pro-inflammatory cytokines such as Interleukin-1β (IL-β), tumor necrosis factor (TNF-α). This hyperresponsive phenotype was not associated with hyperglycemia and could exist independently of periodontitis and may be related to hyperglycemia.

Alley CS, Reinhardt Ra, Maze CA (2003) postulated a genetic basis in the human leucocyte antigen (HLA-DR and HLA- DQ)

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gene regions and /or polymorphisms in the promoter regions of cytokine genes.

There is a class of enzymatically glycated proteins of lipids formatted as a result of chronically elevated serum glucose and lipids in the diabetic state called advanced glycated end products (AGE). It has been suggested that the interaction of AGE with monocytic receptors also contributes to this hyper responsive phenotype through activation of the transcription factor nuclear factor kappa B (NF-κB), increasing gene transcription for proinflammatory cytokines. Other studies concerning the relationship of diabetes and mononuclear cell cytokine production demonstrated that PMN from diabetic patients exhibit a significantly higher production of IL-β. Diabetes also alters the phenotype of the monocyte derived macrophages. Production of essential polypeptide growth factors such as platelet derived growth factor (PGDF) transforming growth factor β (TGFB1) and basic fibroblast growth factor is decreased. Reduced growth factor production at local tissue sites diminishes the repair capacity and the ability to resist proinflammatory cytokine mediated breakdown. (Lalla E *et al*, 2000)

Hyperglycemia

Direct and Indirect Sequelae

Diabetes is a group of metabolic disorders. Deficiency of insulin and impaired cellular sensitivity to insulin (insulin resistance) are defined as types 1 and 2 diabetes, respectively. Impaired glucose tolerance, gestational diabetes and drug- or chemical-induced diabetes, for example, are part of the spectrum of the associated disorders. Regardless of etiology, however, common is the presence of elevated serum glucose. (Lalla E *et al*, 2000)

Direct Consequences of Hyperglycemia

One consequence of elevated levels of glucose is the increased production of sorbitol and fructose by the enzyme aldose reductase. Under homeostatic normoglycemic conditions, this enzyme, which has a low affinity for glucose, usually processes little substrate. However, in hyperglycemia, markedly increased production of sorbitol ensues. This process has long been hypothesized to be linked to the development of diabetic retinopathy, neuropathy and nephropathy. (Lalla E *et al*, 2000)

Indirect Consequences of Hyperglycemia

It is well established that exposure of the body's proteins and lipids to reducing sugars leads to the initial formation of reversible products of nonenzymatic glycation and oxidation products. The best- known of these products is Glycosylated hemoglobinA1c, whose measurement is used as a clinical barometer of glucose control over week to months. After a series of further complex molecular rearrangements, the irreversible advanced glycation end- products (AGEs) are formed. While a range of structures in this heterogeneous class of compounds have been described, such as carboxymethyl (iysine), pentosideine, pyralline and methyglyoxal, for example, the structure responsible for cellular perturbation have yet to be fully delineated AGEs form and accumulate in a number of circumstances, such as ageing, renal failure and diabetes. The presence of AGEs in diabetic plasma and tissues has been linked to the development of diabetic complications. Recent observations that polyglycol metabolites themselves may lead to generation of AGEs suggest that, not unexpectedly, seemingly diverse pathways may converge to form these modified adducts. Accumulation of AGEs in the tissues may result in significant alteration of normal cellular composition and structure. Cross-linking of long-lived proteins such as collagen, for example, may lead to abnormal barrier function and integrity, as well as the trapping of macromolecules, such as low density lipoproteins. In addition, nonenzymatic glycoxidation of basement membrane -associated structures may prevent their facilitation of cell attachment, and modification of growth factors may suppress mitogenic activity. In addition to apparently receptor- independent mechanisms, AGEs may also interact directly with cell surfaces. While a number of Putative cell surface binding sites for AGEs have been indentified, the best characterized of these is the receptor for AGE (RAGE), a member of the immunoglobulin superfamily of cell surface molecules. Molecular cloning of RAGE and the putative hydropathy plot revealed that RAGE Consists of a 332-amino-acid extracellular region containing one "V"-type immunoglobulin domain, followed by two "C"-type domains. This portion of the molecule is followed by a hydrophobic transmembrane spanning domain, and, lastly, by a highly-charged cytosolic tail of 42 amino acids, which is essential for RAGE-mediated signal transduction. (Lalla E *et al*, 2000)

The Receptor for Age and Target Cell Dysfunction

The interaction of AGEs with RAGE perturbs specific cellular function. In homeostasis, RAGE is present at low levels in a number of cell types, including endothelial cells, smooth muscle cells, neurons and monocytes. However, in perturbed states, such as diabetes, renal failure, Alzheimer's disease, and inflammation, for example, the expression of RAGE on critical target cells is strikingly enhanced. (Lalla E *et al*, 2000)

Endothelial Cells

Rage is present at low levels on endothelial cells under normal conditions; upon perturbation, however, the expression of Rage is increased. Ages bind to cultured endothelial cells with Kd-50 nM, in a RAGE- dependent manner leading to vascular lesion in diabetes. Interaction between AGEs and endothelial RAGE lead to increased monolayer permeability and increased production of vascular cell adhesion molecule-1. These processes are blocked by either anti-RAGE IgG or sRAGE. In vivo, infusion of Ages into normal mice result in increased production of interleukin, another mediator closely associated with the development of cellular perturbation. (Lalla E *et al*, 2000)

Mononuclear Phagocytes

AGEs bind to human peripheral blood derived mononuclear phagocytes with Kd.50 Nm. Further the interaction of AGEs with monocyte RAGE resulted in enhanced chemotaxis of monocytes, while soluble AGEs resulted in directed chemotaxis of monocytes. When AGEs are immobilized on the surface of upper membranes in a modified chemotaxis chamber, monocytes are retained. This occurs in a RAGE dependant manner. Interaction between AGEs and monocyte RAGE further results in their activation. (Lalla E *et al*, 2000)

Fibroblasts

Studies have also indicated that RAGE is present on cultured human fibroblasts. Incubation of fibroblasts with AGE α 2-microglobulin resulted in decreased production of type 1 procollagen messenger RNA in a time and dose dependant manner .This did not occur in the presence of anti-RAGE IgG, but was seen when nonimmune IgG was added to the cultures .Similarly the synthesis of type 1 collagen was decreased in the Supernatants of AGE α 2-microglobulin-treated fibroblasts in a RAGE dependent manner as exemplified by experiments with anti- RAGE IgG. These studies suggested that AGE-RAGE interaction may be an important contributory factor in impaired remolding of connective tissue observed in diabetes. (Lalla E *et al*, 2000)

AGEs accumulate in human diabetic gingiva, similar to trends observed in a range of other tissues. Significantly increased AGE levels were identified by enzyme -linked immunosorbent assay in the gingival extracts from diabetic patients, compared with non- diabetic controls. Consistent with these finding, increased AGE- immunoreactive epitopes were identified by immunohistochemistry within the vasculature and connective tissue of human diabetic gingival, compared with that observed in gingival from non- diabetic patients. In adjacent oxidant stress, was evident in diabetic gingival tissue when compared to tissue from non-diabetic periodontitis patients. This data, therefore, suggested that enhanced accumulation of AGEs and increased oxidant stress in human diabetic gingival tissue might play a role in the pathogenesis of diabetes-associated periodontitis. (Lalla E *et al*, 2000)

Lalla E, Lamster IB, Feit M, Huang L, Schmidt AM (1998) conducted a study in which they rendered male C57BL/6J mice diabetic with streptozotocin, a model of relative insulin deficiency or type 1 diabetes. Control mice were treated with citrate buffer alone. One mouth after documentation of diabetes or non diabetic control state, mice were inoculated with the human periodontal pathogen porphyromonas gingivalis, strain 381, or treated with vehicle (phosphate-buffered saline). At 2 and 3 month after infection, increased alveolar bone loss and collagenolytic activity were demonstrated in p. gingivalis-infected, diabetic versus non- diabetic mice. They found that enhanced formation and accumulation of AGEs and vascular and monocytes expression of RAGE were demonstrated in diabetic gingiva by immunohistochemistry.

Thus increased accumulation of AGEs and their interaction with RAGE in diabetic gingiva leads to vascular dysfunction with hyperpermeability, and loss of effective tissue integrity and barrier function. Increased tissue AGEs within the gingiva may serve as a locus for the attraction, immobilization and activation of mononuclear phagocytes, critical mediators in the generation of proinflammatory cytokines and matrix gingiva may ensue from vascular activation, with enhanced expression of adhesion molecules. Activated fibroblasts, in addition to potentially producing further tissue destructive mediators, may also demonstrate diminished reparative responses, with AGE-enriched environment, exaggerated and sustained inflammatory responses ensue in a RAGE-dependent manner. When further superimposed on a setting of impaired reparative responses, destructive periodontal disease result.(Iacopino AM, 1995)

Potential Linkages between Periodontitis and Diabetes

Chronic inflammatory periodontal disease represents a primarily anaerobic gram negative oral infection that leads to gingival inflammation, destruction of periodontal tissue, loss of alveolar bone eventual exfoliation of teeth in severe cases. Certain organisms within the dental plaque are major etiologic agents of periodontitis. These micro organisms produce endotoxins in the form of lipopolysaccharides (LPS) that are instrumental in generating a host mediated tissue destructive host response. (Iacopino AM, 2001)

Infection And Hyperlipidaemia

Studies in humans and baboons show that a number of cytokines are produced in response to systematic LPS exposure. Two of these are TNF α and IL- β. These exert effect on lipid metabolism by influencing production of other cytokines, altering hemodynamic amino acid utilization of various tissues involved in lipid metabolism or modifying the hypothalamic pituitary adrenal axis, increasing plasma concentrations of adrenocorticotrophic hormone, cortisol, adrenaline, noradrenaline, and glucagons. Thus, through action of TNF - α, IL- β exposure to microorganisms results in elevated levels of free fatty acids (FFA), LDL and TRG. These elevations arise from enhanced hepatic lipogenesis, increased adipose tissue lipolysis / blood flow, increased synthesis or reduced clearance of TRG and reduced clearance of LDL due to reductions in lipoprotein lipase activity. In the case of periodontitis elevations of these cytokines may be mediated by systemic dumping of locally produced IL-β / TNF- α and or low level asymptomatic bacteremia / endotoxemia. (Iacopino AM, 2001)

Infection and Insulin Resistance

Although the pathogenesis is poorly understood, it is generally accepted that infection result in a state of insulin resistance and that bacterial LPS has a significant effect on insulin sensitivity. Elevated levels of IL- β are thought to play a role in the development of type I diabetes. It has been demonstrated that IL- β facilitates protein kinase C activation leading to pancreatic β cell destruction through apoptotic mechanisms. Additionally IL- β is cytotoxic to β cell in culture and in animal models through depletion of cellular stores and production of nitric acid.

TNF- α has also been implicated as a causative factor in insulin resistance and type 2 diabetes in animal models and human studies. Elevated levels of TNF- α alter cellular insulin signaling by inhibiting the tyrokinase activity of the insulin receptor and reduce synthesis of the insulin responsive glucose transporter. This creates an insulin resistance syndrome similar to the resistance seen in type 2 diabetes.

TNF- α has also been implicated in the development of macrophage dependent cytotoxicity of pancreatic islets in diabetes. Thus infection induced insulin resistance syndromes if long standing or chronic are considered to be precursors to active diabetes due to the pancreatic β cell destruction that results from sustained elevation of IL- α / TNF- β.

Investigators suggest that proinflammatory cytokines such as IL- β and TNF- α produced as systemic response to periodontal infection are responsible for insulin resistance and subsequent

poor glycemic control in periodontitis patients. (Iacopino AM, 2001)

Iacopino AM, 1995 proposed an explanation for the severe and rapidly progressive periodontitis observed in many diabetic patients. Exaggerated proinflammatory monocytic responses to LPS, enhanced PMN production may be related to diabetes-induced elevation in serum lipid levels resulting in extremely high levels of serum pro- inflammatory cytokines, further elevation of serum lipids, and an even greater reduction of tissue repair capacity. Initial studies demonstrating that periodontitis itself elevates serum lipid levels and recent studies by other demonstrating that within diabetics, the degree of monocytic hyper responsiveness is directly related to the severity of periodontitis certainly support this view.

Oxidative Stress

Advanced oxidation protein product and pentosidine are two important markers of oxidative stress implicated with the pathogenesis in diabetic complications. Nitric oxide plays an important role in human physiology. It is an imperative regulator and mediator in nervous, immune and cardiovascular systems. Nitric oxide level was observed to be lower in diabetic subjects compared to control. Nitric oxide, a pH dependent enzyme is produced from L-arginine due to the enzymatic activity of nitric oxide synthase (NOS). Oxygen is a cofactor for the activity of NOS. In the absence of sufficient oxygen, the functioning of the enzyme NOS becomes affected and consequently, less nitric oxide is produced. Circulation of oxygen in the blood flow is highly impaired in diabetic patients. (Chakraborty A, *et al*., 2010)

CONCLUSION

Proper use of the knowledge of potential relationship between periodontal disease and systemic health requires the dental professional to expand his/her horizons, to step back from the technically demanding aspects of the dental art, and to recognize the oral cavity as one of the many interrelated organ system. Periodontitis usually tends to be a silent disease, until destruction results in acute symptoms. Most patients and medical professionals do not recognize the potential infection that may exist within the oral cavity. Many patients do not know that occult periodontal infections can have the same effect as clinically evident infection. It is upto the dentist to diagnose periodontal infection, provide appropriate treatment and prevent disease recurrence or progression.

References

1. Corbella S, Francetti L, Taschieri S, De Siena F, Fabbro MD.(2013) Effect of periodontal treatment on glycemic control of patients with diabetes: a systematic review and meta-analysis. *J Diabetes Invest*; 4(5):503-9.
2. Gurav AN.(2012) Periodontal Therapy-an adjuvant for glycemic control. *Diabetes Metab Syndr*; 6(4):218-23.
3. Iacopino AM.(1995) Diabetic periodontitis: possible lipid induced defect in tissue repair through alteration of macrophage phenotype and function. *Oral Dis*; 1: 214-299.
4. Lalla E, Lamster IB, Feit M, Huang L, Schmidt AM.(1998) A murine model of accelerated periodontal disease in diabetes. *J periodontal Res* 33: 387-399.
5. Lalla E, Lamster IB, Drury S, Fu C, Schmidt AM.(2000) Hyperglycemia, glycoxidation and receptor for advanced glycation end products: potential mechanisms underlying diabetic complications, including diabetes-associated periodontitis. *Periodontology* 2000; 23: 50-62.
6. Alley CS, Reinhardt Ra, Maze CA.(2003) HLA-D and T lymphocyte reactivity to specific periodontal pathogens in type I diabetic periodontitis. *J Periodontal*; 64: 974-979.
7. Salvi GE, Collins JC. (1997) Monocytic TNF- α Secretion patterns in IDDM patients with periodontal disease. J Clin Periodontal; 24: 8-16.
8. Rathod SR, Raj A, Jadhav P, Sarda T.(2016) Assessment of cytogenic damage in chronic periodontitis and type 2 diabetes mellitus subjects through micronucleus test. *Saudi Journal of Oral Sciences* Jul 1;3(2):75.
9. Iacopino AM.(2001) Periodontitis and diabetes interrelationship: role of inflammation. *Annals Periodontal* ; 6: 125-137.
10. Wright D, Muirhead V, Weston-Price S, Fortune F. (2014) Type 2 diabetes risk screening in dental practice settings: a pilot study. *Br Dent J*; 216: E15.
11. Choi SS, Cha BY, Lee YS, *et al*. (2009) Magnolol enhances adipocyte differentiation and glucose uptake in 3T3-L1cells. Life Sci
12. Dye B A. Global periodontal disease epidemiology. *Periodontol* 2000 2012
13. Preshaw P M, Alba A L, Herrera D *et al*. (2012) Periodontitis and diabetes: a two-way relationship. Diabetologia;
14. Sandhu HS, Hosein YK. (2016) Relationship between Type 2 Diabetes and Periodontitis: Recommendation for Diabetes Screening In Specialty Periodontal Practices. *J Dent & Oral Disord*.; 2(1):1005.
15. Chakraborty A, *et al*. (2010) Effect of metformin on oxidative stress, nitrosative stress and inflammatory biomarkers in type 2 diabetes patients. *Diab Res Clin Pract*
16. American Academy of Periodontology.(1999) The pathogenesis of periodontal diseases (informational paper). *J Periodontol*; 70:457-70.
17. Chapple IL, Matthews JB.(2007) The role of reactive oxygen and antioxidant species in periodontal tissue destruction. *Periodontol* 2000; 43:160-232 (review).
18. Engebretson S, Chertog R, Nichols A, Hey-Hadavi J, Celenti R, Grbic J.(2007) Plasma levels of tumour necrosis factor-alpha in patients with chronic periodontitis and type 2 diabetes. *J Clin Periodontol*; 34: 18-24.
19. Taylor J J, Preshaw P M, Lalla E.(2013) A review of the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J Clin Periodontol*; 40 (Suppl 14): S113-134.
20. Soskolne WA and Klinger A. (2001) The relationship between periodontal disease and diabetes: an overview. *Annals Periodontal* 2001; 6: 91-98.