Periodontitis: An Emerging Risk Factor for Diabetes

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ABSTRACT

The emerging field of periodontal medicine offers new insights into the concept of the oral cavity as one system interconnected with the whole human body. Thus, periodontists of the future will need to understand routine medical diagnostic tests used to monitor patients with systemic conditions that are modified by oral infection. The impact of oral infection on systemic health thus further defines the new branch of periodontology termed periodontal medicine. There are various recent scientific evidences suggesting moderate untreated periodontitis may affect an individual systemically, and may contribute to cardiovascular disease, diabetes. This means a two-way relationship in which periodontal disease in an individual may be a powerful influence on an individual's systemic health or disease as well as the more customarily understood role that systemic disease may have in influencing an individual's periodontal health or disease. Logically included in this definition would be new diagnostic and treatment strategies that recognize the relationship between periodontal disease and systemic disease.

Key words: *Periodontitis, Diabetes mellitus, Inflammatory markers, Glycemic control*

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INTRODUCTION

Diabetes mellitus is a clinical syndrome characterized by hyperglycemia due to an absolute or relative deficiency of insulin. Dysregulation of protein and lipid metabolism also occurs. Patients suffering from DM are known to have increased susceptibility to certain infections. Infections, as they lead to poor metabolic control in diabetes, are of great concern since it has been shown that hyperglycaemia and poor metabolic control result in increased diabetic complications of the eye, kidney and nerves[1].

CLASSIFICATION

I. Type 1 Diabetes Mellitus

Type 1 diabetes, results from autoimmune destruction of insulin - producing β-cells in the pancreas, leading to total loss of insulin secretion. Insulin is used by the body to facilitate the transfer of glucose from the bloodstream into the target tissues, such as muscle, where glucose is used for energy. Because a person with type 1 diabetes no longer produces endogenous insulin, glucose is unable to enter target cells and remains in the bloodstream, resulting in sustained hyperglycemia. A patient with type 1 diabetes must take exogenous insulin to remain alive. Hence, the former name "insulin-dependent diabetes."[1]

II. Type 2 Diabetes Mellitus

This form of diabetes was previously defined as noninsulin- dependent diabetes. It is now known that type 2 diabetic patients have insulin resistance, which alters the utilization of endogenously produced insulin at the target cells. Type 2 patients have altered insulin production as well. Type 2 diabetes commonly occurs in subjects who are insulin-resistant, but these two factors alone are insufficient to cause diabetes unless accompanied by impairer cell function.[1]

PATHOGENESIS OF TYPE 2 DIABETES[1]

1. Insulin resistance

Increased hepatic production of glucose and resistance to the action of insulin in muscle are invariable in both obese and non-obese patients with type 2 diabetes. Insulin resistance may be due to any one of the three general causes:

- ✓ An abnormal insulin molecule
- ✓ An excessive amount of circulating antagonist
- ✓ Target tissue defects.

The last is the most common cause of insulin resistance in type 2 diabetes and seems to be the predominant abnormality in those with more severe hyperglycaemia. A characteristic feature of type 2 diabetes is that it is often associated with other medical disorders including obesity, hypertension and hyperlipidaemia. This cluster of conditions, all of which predispose to cardiovascular disease, is a specific entity, with insulin resistance being the primary defect.

FEATURES:

- Type 2 diabetes or impaired glucose tolerance
- Hypertension
- Low HDL cholesterol; elevated triglycerides
- Central (visceral) obesity
- Microalbuminuria
- Increased fibrinogen
- Increased plasminogen activator inhibitor-1

2. Pancreatic beta cell failure

In type 2 diabetes there is only moderate reduction in the total mass of pancreatic islet tissue which is consistent with a measurable fall in plasma insulin concentration when related to the blood glucose level. Some pathological changes are typical of type 2 diabetes, the most consistent of which is deposition of amyloid. This is accompanied by atrophy of the normal tissue, particularly islet epithelial cells. Islet amyloid is composed of insoluble fibrils formed from islet amyloid polypeptide. Small quantities of islet amyloid are very common in elderly non-diabetic patients, and the role of islet amyloid in the pathogenesis of type 2 diabetes is uncertain. Deposition of amyloid is probably not a cause of diabetes but rather reflects a pathological process which is increased in type 2 diabetes. More extensive amyloidosis is found in patients who have progressed to insulin replacement therapy, suggesting that islet function may become compromised by amyloid deposition.

While beta cell numbers are reduced by 20-30% in type 2 diabetes, alpha cell mass is unchanged and glucagon secretion is increased, which may contribute to the hyperglycaemia. Insulin resistance tends to raise blood glucose and this stimulates insulin secretion to prevent hyperglycaemia. When the maximal insulin secretory capacity has been exceeded, any further increase in fasting blood glucose levels causes a decline in insulin generation. Possible mechanisms for beta cell decom-pensation include glucotoxicity, an intrinsic failure of insulin production, a switch to abnormal processing pathways producing biologically inactive products and chronic degranulation of the beta cell. Some people with type 2 diabetes, most of whom are not overweight, have advanced pancreatic beta cell failure at the time of presentation and require early treatment with insulin.[2]

I. IDIOPATHIC DIABETES

Some forms of type 1 diabetes have no known aetiologies. These patients have no evidence of autoimmunity, permanent insulinopenia and are prone to ketoacidosis. This only represents a minority of patients with type 1 diabetes and the majority of these patients are of African or Asian ancestry. This form of diabetes is strongly inherited, lacks immunological evidence for b-cell autoimmunity, and is not human leukocyte antigen-associated.[3]

II. GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus is defined as glucose intolerance, which is first recognized during pregnancy. It complicates 4% of all pregnancies in the U.S., resulting in 1,35,000 cases annually.[3]

Periodontal disease and diabetes mellitus are closely associated and are highly prevelant chronic diseases with many similarities in pathobiology. Severe periodontal disease often coexists with severe diabetes mellitus. Diabetes is a risk factor for severe periodontal disease. The converse possibility that periodontal disease either predisposes or exacerbates the diabetic condition has received more and more attention. Periodontal disease is considered to the sixth complication of diabetes. Periodontal disease may serve as initiators or propagators of insulin resistance thereby aggravating the glycemic control.

BI-DIRECTIONAL RELATIONSHIP: DIABETES AND PERIODONTAL DISEASES

The cells involved in immunoinflammatory response to bacteria between people with diabetes and those without diabetes, including neutrophils, monocytes and macrophages, is altered in many people with diabetes. The adherence, chemotaxis and phagocytosis of neutrophils often are impaired. These cells are the first line of host defense, and inhibition of their function may prevent destruction of bacteria in the periodontal pocket, thereby increasing periodontal destruction.[4,5,6,7]

Other immunoinflammatory responses are upregulated in people with diabetes. For example, macrophages and monocytes often exhibit elevated production of proinflammatory cytokines and mediators such as tumor necrosis factor α (TNF-α) in response to periodontal pathogens, which may increase host tissue destruction. Elevated TNF-α levels are found in the blood and gingival crevicular fluid, suggesting both a local and systemic hyperresponsiveness of this immune cell line. In a study of subjects with diabetes and periodontitis[8,9,10], Engebretson and colleagues found that crevicular fluid levels of interleukin 1 β (IL-1β) were almost twice as high in subjects with HbA1c levels greater than 8 percent compared with subjects whose HbA1c levels were less than or equal to 8 percent.[1]

- **ALTERED WOUND HEALING**

Altered wound healing is a common problem in people with diabetes. The primary reparative cell in the periodontium, the fibroblast, does not function properly in high-glucose environments.[11] Furthermore, the collagen that is produced by these fibroblasts is susceptible to rapid degradation by matrix metalloproteinase enzymes, the production of which is elevated in diabetes.[12] Thus, periodontal wound healing responses to chronic microbial insult may be altered in those with sustained hyperglycemia, resulting in increased bone loss and attachment loss.

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.[13] AGEs are a primary link between numerous diabetic complications, because they induce marked changes in cells and extracellular matrix components. These changes, including abnormal endothelial cell function, capillary growth and vessel proliferation, also occur in the periodontium of some people with diabetes.

The accumulation of AGEs in patients with diabetes also increases the intensity of the immunoinflammatory response to periodontal pathogens, because inflammatory cells such as monocytes and macrophages have receptors for AGEs. Interactions between AGEs and their receptors on inflammatory cells result in the increased production of proinflammatory cytokines such as IL-1β and TNF-α. This interaction may be the cause of the marked elevation in gingival crevicular fluid levels of IL-1β 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 diseases found in numerous studies of populations of people with diabetes.

MECHANISMS AFFECTING LEVEL GLYCEMIA

Both periodontal diseases and diabetes, especially type 2 diabetes, have major inflammatory components. Chronic periodontal diseases also have the potential to exacerbate insulin resistance and worsen glycemic control, while periodontal treatment that decreases inflammation may help diminish insulin resistance.

Patients with inflammatory periodontal diseases often have elevated serum levels of proinflammatory cytokines. In patients with diabetes, hyper-inflammatory immune cells can exacerbate the elevated production of proinflammatory cytokines which causes inhibition of auto phosphorylation of insulin receptors and suppression of second messanger signalling by inhibiting enzyme tyrosine kinase, leading to insulin resistance which causes decrease cellular uptake of glucose, leading to hyperglycemia, poor glycemic control and further complications . It also may explain the research showing a greater risk of poor glycemic control in patients with diabetes who have periodontitis compared with that in patients with diabetes who do not have periodontitis, as well as the research showing improvement in glycemic control after periodontal therapy in some patients with diabetes.[3]

In a recent study of subjects with type 2 diabetes and periodontitis, Iwamoto and colleagues found that periodontal treatment resulted in a significant reduction in serum levels of TNF-α that was accompanied by a significant reduction in mean HbA1c values (from 8.0 to 7.1 percent). The improvement in HbA1c values was correlated strongly with the reduction in serum TNF-α levels across the patient population. This suggests that a reduction in periodontal inflammation may help decrease inflammatory mediators in the serum that are associated with insulin resistance, thereby improving glycemic control.[14]

EVIDENCES:

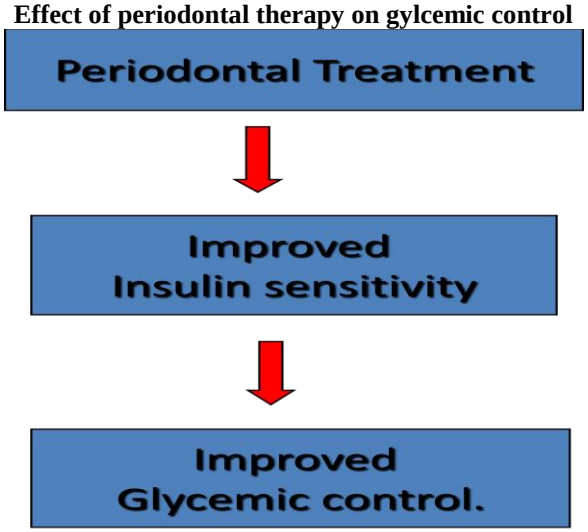
Albridge JP, Lester V, Watts TL et al (1995)[15] conducted a study on 32 diabetic patients, dental indices were examined and patients were given mechanical therapy. They found that individuals with moderately well controlled or well controlled diabetes and periodontitis who are treated by mechanical therapy alone may demonstrate no significant changes in glycemic control despite involvement in their periodontal health. Also in studies of subjects treated by mechanical therapy without adjunctive use of antibiotics, significant changes in glycemic control are less common. Taylor GW, Burt BA et al (1996)[16] conducted a longitudinal study on 700 patients with Type 2 (non insulin dependent) diabetes, and found that severe periodontitis was associated with significant worsening of glycemic control over time. Individuals with severe periodontitis at baseline examination had a greater incidence of worsening glycemic control over a 2-4 year period than did those without periodontitis at baseline.

Thorstensson H, Kuylenstierna J, Hugoson A (1996)[17] Suggested that periodontitis has also been associated with the classic complications of diabetes. They conducted a study on 91 diabetic patients and found that diabetic adults with severe periodontitis at baseline had a significantly greater incidence of kidney and macrovascular complications over the subsequent 1 to 11 years than diabetic adults with only gingivitis or mild periodontitis. They concluded that severe periodontitis preceded the onset of clinical diabetic complications in these subjects. Mealey BL (2000)[18] conducted a study on 30 diabetic patients with periodontitis and were given mechanical debridement therapy. They found that in diabetic patients with periodontitis, periodontal therapy may have effects on glycemic control. This is especially true for patients with poor glycemic control and more advanced periodontal destruction before treatment.

Iwamoto Y, Chuang S, Moon JY et al (2001)[19] conducted a study on 13 type 2 diabetic subjects with periodontitis. They found that periodontal treatment consisting of mechanical debridement and local delivery of Minocycline resulted in a significant reduction in serum TNF-α levels along with reduction of glycocylated hemoglobin from 8.0% to 7.1%. Grossi SG, Mealey BL, Rose LF et al (2004)[20] conducted a study on 45 diabetic patients, their periodontal examination were conducted. They concluded that chronic gram negative periodontal infections cause persistent systemic challenge with periodontopathic bacteria and their products leading to systemic infection

Saremi A, Nelson RG, Reid MT (2005)[21] conducted a prospective longitudinal study of 628 subjects aged ≥35 years, examined the effect of periodontal disease on overall and cardiovascular disease mortality in Pima Indians with type 2 diabetes. Periodontal abnormality was classified as no or mild, moderate, and severe, based on panoramic radiographs and clinical dental examinations. They found that subjects with severe periodontal disease had 3.2 times the risk of cardio-renal mortality (IHD and diabetic nephropathy combined) compared with the reference group (no or mild periodontal disease and moderate periodontal disease combined. Wijnand JT, Victor EA, Bruno G et al (2010)[22] conducted a literature search. A total of 371 patients were included in this analysis with periodontitis. The duration of follow-up was 3–9 months. All studies described a research population of type 2 diabetic patients in whom glycemic control improved after periodontal therapy compared with the control group. It concluded that periodontal treatment leads to an improvement of glycemic control in type 2 diabetic patients for at least 3 months.

Effect of periodontal therapy on gylcemic control



CONCLUSION

Epidemiological studies have suggested that successful anti-microbial therapy might result in improved insulin resistance in highly insulin resistant patients. Because it has been currently considered that the major contributing factor for insulin resistance is the release of pro-inflammatory cytokine, tumour necrosis factor-alpha (TNF-alpha) due to periodontal inflammation. So patients should be strictly treated with non-surgical periodontal therapy and their serum TNF-alpha levels should be periodically monitored to avoid further systemic complication due to persistent release of inflammatory cytokines.[23,24,25]

REFERENCE:

1. Brain L. Maelay, Gloria L. Ocampo. Diabetes mellitus and periodontal disease.*Periodontology* 2000, 2007;44: 127–153
2. Scannapieco FA. Role of oral bacteria in respiratory infection. *J Periodontol* 1999; 70 : 793.
3. Engebretson SP, Hey-Hadavi J, Ehrhardt FJ, et al. Gingival crevicular fluid levels of interleukin-1β and glycemic control in patients with chronic periodontitis and type 2 diabetes. *J Periodontol* 2004; 75(9):1203-8.
4. Lo¨e H, Anerud A, Boysen H, Smith M. The natural history of periodontal disease in man. The rate of periodontal destruction before 40 years of age. *J Periodontol* 1978: 49: 607–620. 5. Lo¨e H, Anerud A, Boysen H, Smith M. The natural history of periodontal disease in man. Tooth mortality rates before 40 years of age. *J Periodontal Res* 1978: 13: 563–572.
5. Lo¨e H, Anerud A, Boysen H, Smith M. The natural history of periodontal disease in man. Study design and baseline data. *J Periodontal Res* 1978: 13: 550–562.
6. Mealey BL, Oates TW. Diabetes mellitus and periodontal diseases. *J Periodontol* 2006: 77: 1289–1303.
7. Socransky SS, Haffajee AD. The bacterial etiology of destructive periodontal disease: current concepts. *J Periodontol* 1992: 63: 322–331.
8. Preshaw PM. Periodontal disease and diabetes. *J Dent* 2009: 37: S575–S577.
9. Ryan ME, Carnu O, Kamer A. The influence of diabetes on the periodontal tissues. *J Am Dent Assoc* 2003: 1: 34S–40S.
10. Zamirian M, Raoofi S, Khosropanah H. Relationship between Periodontal Disease and Acute Myocardial Infarction. *Iranian Cardiovascular research journal* 2008;4: 216-22.
11. Golub LM, Lee HM, Ryan ME. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv Dent Res* 1998;12(2):12-26.
12. Katz J, Bhattacharyya I, Farkhondeh-Kish F, Perez FM, Caudle RM, Heft MW. Expression of the receptor of advanced glycation end products in gingival tissues of type 2 diabetes patients with chronic periodontal disease: a study utilizing immunohistochemistry and RTPCR. *J ClinPeriodontol* 2005; 32(1):40-4.
13. Vettore MV, Lea˜o AT, LealMdo C, Feres M, Sheiham A. The relationship between periodontal disease and preterm low birthweight : clinical and microbiological results. *J Periodont Res* 2008; 43: 615–626.
14. Aldridge JP, Lester V, Watts TL, Collins A,Viberti G, Wilson RF.Single-blind studies of the effects of improved periodontal health on metabolic control in type 1 diabetes mellitus. *J ClinPeriodontol* 1995; 22(4):271-275.
15. Taylor GW, Burt BA, Becker MP,Genco RJ, Sholossman M, Khowler WC et al. Severe periodontitis and risk for poor glycemic control in patients with non-insulin-dependent diabetes mellitus.*J Periodontol*. 1996; 67:1085-93.
16. Thorstensson H, Kuylenstierna J, Hugoson A. Medical status and complications in relation to periodontal disease experience in insulin-dependent diabetics. *J ClinPeriodontol*. 1996; 23:194-202.
17. Mealey BL, Oates TW. Diabetes Mellitus and Periodontal disease. *J Periodontal* 2006; 77:1289.
18. Mealey BL: Diabetes Mellitus. In Rose LF, Genco RJ, Mealey BL, et al .Periodontal Medicine, 2000, BC Decker.
19. Grossi SG, Mealey BL, Klokkevold PR. Periodontal Medicine: Impact of periodontal infection on systemic

health. Carranza's Clinical Periodontology.10th edition: 312-329.
20. Saremi A, Nelson RG, Reid MT, Hanson RL, Siewer ML, Taylor GW et al. Periodontal disease and mortality in TYPE 2 Diabetes. *Diabetes care* 2005; 28: 27-32.
21. Wijnand J. Teeuw, Victor E.A. Gerdes, Bruno G. Loos. Effect of periodontal Treatment on Glycemic Control of Diabetic Patients – A systemic review and meta-analysis. *Diabetes Care*. 2010; 33: 421–427.
22. Lamster IB, Lalla E, Borgnakke WS, Taylor GW. The relationship between oral health and diabetes mellitus. *J Am Dent Assoc* 2008: 139(Suppl.): 19S–24S.
23. Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006: 17: 4–12.
24. Arrieta-Blanco JJ, Bartolome-Villar B, Jimenez-Martinez E, Saavedra-Vallejo P, Arrieta-Blanco FJ. Dental problems in patients with diabetes mellitus (II): gingival index and periodontal disease. *Med Oral* 2003: 8: 233–247.