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Review Article

Role of Periodontal Disease as a Risk Factor for Diabetes Mellitus

Prathush Ajith Kumar[1], Samba Siva Reddy[1]*, Krishna Kripal[2], Harisha KB[3] and Sruthi K Nair[1]

[1]Post Graduate Student, Department of Periodontology, Rajarajeswari Dental College and Hospital, Bangalore, Karnataka, India

[2]Professor, Department of Periodontology, Rajarajeswari Dental College and Hospital, Bangalore, Karnataka, India

[3]Department of Orthodontics, Dayananda Sagar College of Dental Sciences, Bangalore, Karnataka, India

***Corresponding Author:** Samba Siva Reddy, Post Graduate Student, Department of Periodontology, Rajarajeswari Dental College and Hospital, Bangalore, Karnataka, India.

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Abstract

The presence of periodontal disease in persons with diabetes mellitus may also lead to poor glycemic control. Inflammatory mediators produced by the periodontal tissues, triggered by periodontal organisms, enter the systemic circulation. These mediators, including TNF-alpha and IL-6, likely contribute to insulin resistance. Also, these inflammatory mediators, as well as bacterial products such as LPS, once gaining access to the blood stream, have effects on distant organs through induction of acute phase proteins such as CRP, fibrinogen, and serum amyloid A. These factors are often elevated in the plasma of periodontal patients and can cause harmful effects on the heart, kidneys, and other organs. Significantly increased mortality and morbidity from heart and kidney disease has been documented in patients with type 2 diabetes mellitus who have periodontal disease.

Keywords: *Diabetes Mellitus; Periodontal Diseases; Periodontits; Glycemic Control*

Introduction

Recognition of subgingival plaque as a microbial biofilm has substantially added to our understanding of the pathophysiology of periodontal disease. In microbial biofilms, bacteria are embedded in an extracellular matrix and adhere to one another and/or to a surface [1]. Bacterial adhesion is essential to establish the subgingival biofilm, and the pathogenic potential of this biofilm is determined by the growth and maturation of the bacteria in question. These bacteria constantly expel part of their cell structure components into the crevicular space. The cell wall structures of Gram-negative bacteria are of major importance in the pathogenesis of periodontal disease.

These structures are lipo-polysaccharides and vesicles with protein content that form part of the normal turnover of the cell wall of these microorganisms and can activate the innate host response. The structure of the biofilm provides highly favourable conditions for the survival of the bacteria that form it, despite an intact host immune system. The virulence factors of these microorganisms are responsible for triggering the sequence of pathogenic events in periodontal disease. Periodontal micro-organisms, in particular *Porphyromonas gingivalis* (P.g.) and *Tannerella forsythia* (T.f.), were found to increase MMP-9 in gingival crevicular fluid and serum [2].

According to the pathogenic model proposed in (Figure 1), periodontal disease might increase the already elevated cytokine levels in diabetic patients and thereby contribute to systemic inflammation. Excessive formation and accumulation of AGEs in tissues is the most common cause of diabetic complications. The binding of these molecules to neutrophils produces a hyper inflammatory state that amplifies the response to cytokines. These previously activated neutrophils also show a heightened response on making contact with LPS of gram-negative bacteria (e.g., P.g.) in the subgingival biofilm, and the consequent triggering of the inflammatory cascade increases the destruction of periodontal connective tissue and the severity of diabetes mellitus [3].

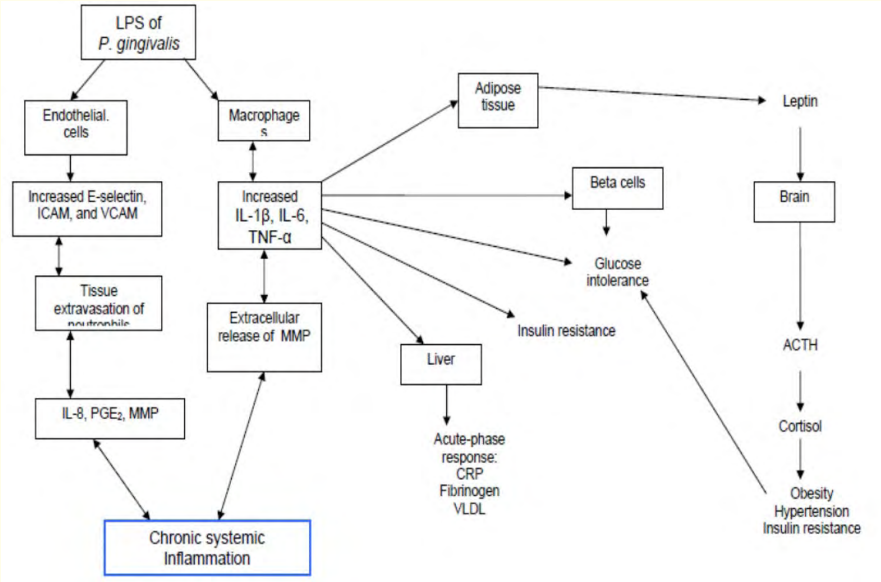

Figure 1: *Model depicting how periodontal infection could contribute to systemic inflammation, impairing sugar balance and diabetes mellitus.*

Periodontal Treatment and Glycemic Control in Diabetics

Although the relationship between diabetes mellitus and periodontal disease is not questioned in the current literature, the effect of the metabolic control of diabetes mellitus on periodontal disease and the effect of periodontal treatment on metabolic control in diabetic patients remains controversial (Table 1) summarizes recent meta-analyses on this issue.

Study Question	Type of research needed
Prevalence of periodontal disease in diabetic populations.	Clinical and epidemiological studies in wide samples of both type-1 and type-2 diabetic patients.
Periodontal disease and metabolic syndrome.	Clinical and epidemiological studies with adequate samples, probably requiring a multi-center approach.
Effect of periodontal treatment on sugar metabolism.	Clinical intervention studies with randomized controlled trial design to assess different treatment modes.
Periodontal pathogens and diabetes.	Clinical, microbiological, and biochemical studies.
Genetics of periodontal disease and diabetes.	Molecular biological studies to assess the role of genetics in the development of the diseases.

Table 1: *Suggestions for future research on periodontal disease- diabetes mellitus.*

In view of the very high prevalence of both diseases and their potentially severe repercussions, the medical specialist should play a leading role in encouraging diabetic patients to visit their dentists regularly to control detrimental factors, such as the sustained presence of bacterial plaque in the periodontal pocket. Likewise, oral health personnel should bear in mind that impaired sugar metabolism and

diabetes mellitus can affect the outcome and severity of periodontal disease outlines the types of study required to advance our knowledge and understanding of this issue.

Does Periodontal Disease Affect Diabetic Complications?

A prospective study of 628 Pima Indians with type 2 diabetes mellitus, the median follow up of which was 11 years, showed a significant increase of the adjusted relative risk for cardio-renal mortality in those with severe periodontitis (odds ratio 3.2) compared with those with no or only mild to moderate periodontitis. In 2012, the American Heart Association reviewed the relationship between periodontal disease and atherosclerotic vascular disease in their scientific statement [4].

They reported that epidemiological and experimental studies showed an association between periodontal disease and atherosclerotic vascular disease. However, they also reported the lack of evidence that treatment of periodontal disease would prevent atherosclerotic vascular disease or modify its outcome. Vascular abnormalities, both macrovascular and microvascular, are characteristic diabetic complications. The relationship between microvascular/macrovascular diabetic complications and periodontal disease might have some similarities with that between cardiovascular disease and periodontal disease. So far, there have been only a small number of studies about the relationship between diabetic macrovascular/ microvascular complications and periodontal disease. Further large-scale clinical studies and pathological animal studies are required [4].

As aforementioned, periodontal disease is accepted as one of the diabetic complications by its high prevalence and severity in diabetes mellitus patients. Additionally, there is a bidirectional relationship between periodontal disease and diabetes mellitus. A recent consensus report of the Joint European Federation of Periodontology and the American Academy of Periodontology (EEP/AA) workshop on periodontitis and systemic disease also discussed a strong relationship between periodontal disease and diabetes mellitus. However, large-scale randomized prospective trials and pathological studies including animal studies are required for further investigation [5].

There is substantial evidence from cross-sectional and prospective studies that people with types 1 and 2 diabetes mellitus have more than double the risk of developing periodontitis; reviewed by Taylor and Borgnakke45. Diabetes mellitus can also result in more severe periodontal destruction than in matched non-diabetes mellitus groups. The increased risk for periodontitis is dependent on glycaemic control and not the duration of diabetes mellitus.

Impact of Periodontitis on Glycaemic Control

A bi-directional relationship between periodontitis and type 2 diabetes mellitus has been suggested with the presence of chronic periodontitis thought to have a reciprocating negative effect on diabetes mellitus control. Early evidence came from studies in a distinct population group of Pima Indians who have a very high prevalence of type 2 diabetes mellitus. These studies indicated that severe periodontal inflammation was predictive of a greater deterioration in glycaemic control over time compared with a non-periodontitis group, and was a strong predictor of mortality from the common diabetes mellitus-associated complications of ischaemic heart disease and diabetic nephropathy [6].

These results could not be directly extrapolated to other population groups due to genetic homogeneity within the Pima Indian group who may be particularly susceptible to hyper-inflammation and derangement in glycaemic control Epidemiological surveys within more diverse population groups have therefore been conducted. A US-based cross-sectional study examined the electronic medical records and dental insurance data of more than 5,000 dually insured people with diabetes mellitus and insurance claims for periodontal care were taken as a proxy measure for periodontitis. Mean glycated haemoglobin (HbA1c) was 7.66 % and was 0.08% higher in the 38.00 % of patients who had received periodontal care, but insufficient information about the periodontal status of participants were available within this study to draw firm conclusions from the results [7].

Many cross-sectional studies have undertaken comprehensive periodontal examination in diabetes mellitus patients although the logistical difficulties of doing so have led to relatively small sample sizes within many studies. A survey of 35 people with type 2 diabetes mellitus (17 with periodontitis matched with 18 without periodontitis) and a larger survey of 181 type 2 diabetes mellitus adults both reported correlations between periodontal status and HbA1c. The severity of periodontitis was an independent predictor of both elevated HbA1c and hsCRP in a group of 140 type 2 diabetes mellitus participants [8].

A large-scale, prospective study has been conducted in Japan that addresses some of the limitations of the smaller studies and had two strands; study 1 examined the risk of developing periodontal pockets in 5,856 participants over five years with baseline HbA1c levels ≥ 6.5%, while study 2 examined 6,125 participants with HbA1c < 6.5% at baseline and determined their relative risk for elevated HbA1c over five years with baseline periodontal status. Relative risk of developing a periodontal pocket was 1.17 times greater in those with HbA1c of ≥6.5% at baseline, confirming the accepted evidence of an increased risk of periodontitis with poor glycaemic control. The risk of having elevated HbA1c (≥ 6.5%) over the five years was increased 2 - 3 fold, depending on the severity of the periodontal lesion at baseline. Periodontitis was also associated with increased risk for diabetes mellitus incidence in a seven-year prospective study of 5,848 non-diabetic individuals but significance was lost when adjusting for confounding factors. HbA1c levels correlated with the surface area of the inflamed periodontal lesions and therefore the extent of periodontal inflammation in one study conducted within a type 2 diabetes mellitus group [9].

Some studies have examined the relationship between periodontal condition and plasma glucose levels; non-diabetics with periodontitis are reported to have higher resting plasma glucose and HbA1c levels than matched controls. Analysis of data from 12,254 participants in the Third National Health and Nutrition Examination Survey (NHANES III), showed that participants with the most severe periodontal destruction had an increased odds ratio for both impaired fasting glucose (≥ 100 but < 126 mg/dl) and diabetes mellitus (≥126 mg/dl) after adjustment for potential confounders [10]. Animal studies (while limited in their ability to provide direct evidence applicable to humans) have confirmed the destabilisation of glycaemic control by periodontal inflammation.

Periodontitis is readily initiated in Wistar rats by the tying of ligatures around teeth for a period of weeks. These periodontitis rats had increased blood glucose compared with non- periodontitis rats. The precise mechanism underlying the effect on glycaemic control by periodontal inflammation has been investigated using this same animal model (n = 48) with half the animals having a ligature applied (periodontitis rats) and the other half remaining as controls. Plasma concentration of TNF-α was higher in periodontitis rats compared with controls. The periodontitis rats group showed decreased insulin sensitivity and insulin signal transduction in adipose and skeletal muscle tissues compared with the control group, which may have been mediated by the increased plasma TNF-α [11].

When taken together, the cross-sectional surveys and prospective studies described above, supported by the limited animal model studies, do offer some compelling evidence of a disruptive influence on glycaemic control by chronic periodontal inflammation. Intervention studies have been conducted to provide further clarity on the relationship between periodontitis and glycaemic control and to explore interventive therapies that may improve the outcome for diabetes mellitus patients. Periodontal therapy involves professional removal of the biofilm and home care instruction to prevent re-accumulation of the plaque bacteria and re-development of the biofilm.

Various studies have been done to determine the prevalence and severity of periodontitis in diabetics. Type1 as well as type 2 diabetes mellitus have been shown to be the major risk factor for the development of periodontal disease in certain population. Study conducted on Gullah African Americans, Hispanic Americans, France, Jorden, Brazil, Srilanka, Iraq and Finland reported higher prevalence of periodontitis in type 2 diabetes mellitus. Landmark studies of Nelson (1990); Emrich (1991) and Taylor (1996) on Pima Indians reported a 2.6, 3 and 4 times amount of periodontal destruction in diabetics when compared with non-diabetics respectively. Further the duration of diabetes mellitus also affects periodontitis which was evaluated by the Juan Cerda G (1994) and Khader Y S (2008) who reported an increase in periodontal tissue destruction when the duration of the diagnosis of type 2 diabetes mellitus was more than five years [12].

Periodontal disease is the most prevalent oral complication in IDDM and NIDDM patients and has been labelled the "sixth complication of diabetes mellitus". Numerous studies have shown both increased prevalence and severity of periodontal disease in patients with IDDM. Diabetic children and adults with less than optimal metabolic control show a tendency towards higher gingivitis scores. Early case reports suggested that diabetic adolescents and teenagers may suffer from periodontitis [13]. In a more recent study, the prevalence of periodontal disease was 9.8% in 263 patients with IDDM, compared with 1.7% in people without diabetes mellitus. Most of the periodontal disease was found in those age 11 - 18 years. However, earlier rapid periodontal destruction was not found in adolescent patients with IDDM in Finland. This difference may be related to different levels of metabolic control in participants of the two studies. For example, case reports suggest a strong relationship between rapid periodontal breakdown and elevated blood glucose levels [14].

Patients with IDDM of > 10 years duration had greater loss of periodontal attachment compared with those of < 10 years duration. This was found to be particularly true for patient's age 35 years. More recently, it was reported that IDDM patient's age 40 - 50 years with long IDDM duration had significantly more sites with advanced periodontal destruction and alveolar bone loss than people without diabetes mellitus. It has also been demonstrated and confirmed that in IDDM patients with retinal changes the loss of periodontal attachment is significantly larger than in IDDM patients without retinal changes [15].

Several studies have clearly demonstrated that IDDM patients with poor long-term control of diabetes mellitus have increased extent and severity of periodontal disease, whereas those who maintain good metabolic control have minimal periodontal problems. Patients with IDDM of long duration who have retinopathy tend to exhibit more loss of periodontal attachment as they reach age 40 - 50 years. Good oral home care and frequent professional check-ups and care are important for these patients. Few studies have dealt with NIDDM subjects. In a study of Pima Indians, 40% of whom have NIDDM, diabetic patients age < 40 years had increased periodontal attachment loss, and alveolar bone loss was associated with increased glucose intolerance [16].

Periodontal tissue loss increased with age and was higher in people with diabetes mellitus compared with people without diabetes mellitus in all age groups. Alveolar bone loss also increased with age and was substantially more frequent in patients with NIDDM compared with nondiabetic people age 5 - 44 years. Toothlessness was 15 times higher in the diabetic than in the nondiabetic group. Indeed, 30% of these young adults with NIDDM had no teeth. The odds ratio for subjects with NIDDM for increased risk of periodontal destruction was 3.43 (95% confidence interval (CI) 2.28-5.16). In this population, the age- and sex-adjusted incidence of periodontal disease in subjects with NIDDM was 75 cases per 1,000 person-years, which was substantially higher than the rate of 29 cases per 1,000 person-years in subjects without diabetes mellitus [17].

Early studies of the pathogenesis of periodontal disease in diabetic patients centered on the general feature of "basement membrane thickening" and possible changes in the vasculature. More recent studies have focused on the role of the periodontal infection, the microflora of dental plaque, collagen metabolism, leukocyte function, and other aspects of the host response. All of these factors may individually or synergistally contribute to periodontal disease.

The reason for the greater occurrence of periodontal destruction in diabetics is not clear. However, studies of the periodontal flora find similar microorganisms in diabetic and nondiabetic people, suggesting that alteration in host responses to periodontal pathogens account for these differences in periodontal destruction. For example, increased susceptibility to infection by periodontal bacteria associated with altered phagocyte functions and reduced healing capacity associated with altered collagen metabolism may explain, in part, the increased levels of periodontal disease in diabetic patients. The response to treatment suggests that the periodontal lesions are eminently treatable and that eradication of the infection and the inflammatory foci may reduce insulin requirements. The knowledge among people with diabetes mellitus of oral co-morbidity is generally poor and suggests the need for appropriate health education and health promotion to improve the oral health of diabetic patients [18].

Conclusion

Periodontal diseases are more prevalent and severe in patients with diabetes mellitus. Compelling evidence demonstrates that diabetes mellitus is a major risk factor for periodontitis regardless of subgingival plaque. Several lines of evidence suggest a potential role of periodontitis in the onset of diabetes mellitus and glycemic control through inflammatory and infectious mechanisms. Treatment of periodontitis in diabetic patients results in a modest but significant reduction in HbA1c levels and thus in better glycemic control. Larger clinical trials are needed to characterize the role of specific periodontal therapies in controling diabetes mellitus.

Bibliography

1. Bascones A., *et al*. "New knowledge of the pathogenesis of periodontal disease". *Quintessence International* 35.9 (2004): 706-716.

2. Janket SJ., *et al*. "Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies". *Journal of Dental Research* 84.12 (2005): 1154-1159.

3. Serrano MCA. "Diabetes mellitus, insuficiencia cardíaca y mortalidad". *Medical Clinics* 125.5 (2005): 182-183.

4. Lockhart PB., *et al*. "Periodontal disease and atherosclerotic vascular disease: does the evidence support an independent association? A scientific statement from the American Heart Association". *Circulation* 125.20 (2012): 2520-2544.

5. Chapple IL and Genco R. "Diabetes mellitus and periodontal diseases: consensus report of the Joint EFP/AAP Workshop on Periodontitis and Systemic Diseases". *Journal of Periodontology* 84.4 (2013): S106-S112.

6. Shultis WA., *et al*. "Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes mellitus". *Diabetes Mellitus Care* 30.2 (2007): 306-311.

7. Spangler L., *et al*. "Cross-sectional study of periodontal care and glycosylated hemoglobin in an insured population". *Diabetes Mellitus Care* 33.8 (2010): 1753-1758.

8. Chen L., *et al*. "Association of periodontal parameters with metabolic level and systemic inflammatory markers in patients with type 2 diabetes mellitus". *Journal of Periodontology* 81.3 (2010): 364-371.

9. Nesse W., *et al*. "Dose-response relationship between periodontal inflamed surface area and HbA1c in type 2 diabetics". *Journal of Clinical Periodontology* 36.4 (2009): 295-300.

10. Choi YH., *et al*. "Association between periodontitis and impaired fasting glucose and diabetes mellitus". *Diabetes Mellitus Care* 34.2 (2011): 381-386.

11. Colombo NH., *et al*. "Periodontal disease decreases insulin sensitivity and insulin signalling". *Journal of Periodontology* 83.7 (2012): 864-870.

12. Anoop Kumar., *et al*. "Prevalence and severity of periodontal diseases in type 2 diabetes mellitus of Bareilly region (India)". *International Journal of Medical Science and Public Health* 2.1 (2013): 77-83.

13. Gusberti FA., *et al*. "Puberty gingivitis in insulin-dependent diabetic children. I Cross-sectional observations". *Journal of Periodontology* 54.12 (1983): 714-720.

14. Ainamo J., *et al*. "Rapid periodontal destruction in adult humans with poorly controlled diabetes mellitus. A report of 2 cases". *Journal of Clinical Periodontology* 17.1 (1990): 22-28.

15. Rylander H., *et al*. "Prevalence of periodontal disease in young diabetics". *Journal of Clinical Periodontology* 14.1 (1987): 38-43.

16. Shlossman M., *et al*. "Type 2 diabetes mellitus and periodontal disease". *Journal of the American Dental Association* 121.4 (1990): 532-536.

17. Nelson RG., *et al*. "Periodontal disease and NIDDM in Pima Indians". *Diabetes Mellitus Care* 13.8 (1990): 836-849.

18. Adams PF and Benson V. "Current estimates from the National Health Interview Survey, 1989". *Vital and Health Statistics, Series 10* 176 (1990): 1-221.

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