

Diabetes as a Risk Factor for Periodontal Disease: Current Status and Future Considerations

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Abstract

Introduction: Over the past decade, there has been an emerging interest in the inter-relationship between systemic conditions and oral health. Diabetes is perhaps one of the best documented conditions that have been closely linked with periodontal disease. This paper reviews the role of diabetes as a risk factor in periodontal disease. The treatment implications in the management of periodontal disease as an integral component of diabetes care is also discussed in light of the current understanding of the pathogenesis of these 2 chronic conditions. **Materials and Methods:** Epidemiological, clinical and laboratory studies examining the relationship between diabetes and periodontal diseases were selected from both medical and dental journals. **Results:** The severity of periodontal destruction has been shown to be related to the direct and indirect effects of glycaemic control, with other factors also being implicated. Although some studies have pointed towards a bi-directional relationship between glycaemic control and periodontal health, it is still not clear if improvement in periodontal health could lead to improved metabolic control. **Conclusion:** Diabetes and periodontal disease are closely related in many ways, though the effect of periodontal disease on diabetes control remain to be determined, with larger intervention studies. In light of the increasing evidence of the relationship between diabetes and periodontal disease, management of oral health should form an integral part of diabetes management.

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Introduction

Diabetes mellitus (DM) is a common and growing global health problem. It is highly prevalent in Asian communities. Hong Kong, Pakistan, and Singapore are among the countries with the highest prevalence of diabetes in the adult population. In Singapore, the prevalence of DM among adult Singaporeans increased from 1.9% in 1975, 4.7% in 1984 and 8.6% in 1992¹ to about 9% in 1998.² However, in the recent National Health Survey 2004, there had been a decline to 8.2%.³

Diabetes is a chronic and complex disease that requires continuous lifelong management to reduce the high morbidity and premature mortality caused by its associated complications. These complications can be reduced, if not completely prevented, with optimal glycaemic control.

However, it was found that about 50% of 1697 Singapore patients surveyed at hospitals and government outpatient clinics had glycated haemoglobin levels in the suboptimal or unacceptable levels.⁴ With poor glycaemic control, the social and financial burden of DM is substantial, as a considerable amount of medical resources are utilised for the management of its many complications, namely, retinopathy, diabetic nephropathy, diabetic foot complications, increased risk of hypertension and dyslipidaemia, and ischaemic heart disease.⁵ DM is the sixth commonest cause of death in Singapore, accounting for 9.3% of all deaths if all diabetes-related deaths are considered.⁶ Thus, early diagnosis and aggressive treatment of the disease can delay or prevent the progression of the major chronic complications as mentioned, due to macrovascular (coronary artery disease)⁷ and microvascular

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diseases (retinopathy, nephropathy, neuropathy).^{8,9} In recent years, there has been an emerging interest in the link between periodontal disease and systemic conditions. Periodontal disease has been cited as the sixth complication of DM.¹⁰ It is clear that the control of diabetes and periodontal disease share a similar platform as they require a high degree of patient compliance. While patients with poor glycaemic control have been found to have more severe periodontal disease, it is not clear if effective control of periodontal disease is associated with a concomitant improvement in glycaemic control.

This paper will review the evidence supporting the link between periodontal disease and glycaemic control in patients with diabetes. It will also address future problems and research directions that would be needed in the study of periodontal disease and diabetes.

Epidemiological Evidence – Glycaemic Control and Periodontal Health

It is generally accepted that periodontal disease is more prevalent and more severe in individuals with diabetes than in non-diabetics. Both epidemiological studies and case reports have shown diabetes to be a major risk factor for periodontitis. Periodontitis has been found to be more prevalent and more severe in patients with diabetes than the normal population. One of the common systemic parameters used in most studies is metabolic control as measured by blood glucose levels or glycated haemoglobin (HbA1c). For subjects with DM, optimal HbA1c level is between 6.5% and 7.0%, with values greater than 8% being unacceptable, requiring some form of intervention.

Some of the earlier studies that showed a relationship between diabetes and periodontal disease were conducted in type 1 diabetes. It was found that these patients presented with more gingival inflammation than their non-diabetic counterparts.¹¹⁻¹³ Periodontal disease severity increased with age, with no gender predilection. Patients with type 1 diabetes (age, 30 to 40 years) had increased periodontal breakdown. Those suffering from type 1 diabetes for more than 10 years had more loss of attachment than those with less than 10 years of history. The duration of DM appears to affect periodontal disease severity. The longer the DM duration, the more extensive the periodontal disease.^{13,14} While insulin dosage did not seem to relate to the degree of periodontal breakdown, type 1 diabetics with retinal changes had greater loss of attachment than others.¹² However, other studies failed to demonstrate such a relationship.¹⁵ One of the largest scale studies to date were carried out in the Pima Indians of the Gila River Indian community in Arizona, who have the highest reported prevalence of type 2 DM in the world. About 50% of them above 35 years of age are affected by the disease.¹⁶ In a cross-sectional survey

of the community, it was found that for all age groups, the Pima Indians with diabetes had higher prevalence of periodontal disease than those without the disease.¹⁷ It is thus concluded that both type 1 and 2 DM are predictors of periodontal disease and periodontal disease is considered a complication of DM. These and other controlled studies reported at least a 2-fold increase in the risk for periodontal disease in diabetics when compared with healthy controls.¹⁸⁻²²

Tervonen and Knuuttila²³ revealed that well-controlled diabetic subjects had better periodontal health than the controls. In a later study, Tervonen and Oliver²⁴ reported an increase in prevalence, severity and extent of periodontitis with poorer metabolic control. The extent of calculus increased as well with poorer control. In recent studies,^{25,26} other authors also reported greater prevalence and more severe periodontal disease in DM subjects. Poorer glycaemic control was found to be associated with elevated gingival crevicular fluid interleukin-1 β (IL-1 β), which may explain the association between poor glycaemic control and more advanced periodontal disease.²⁷

Taylor et al²⁸ did a longitudinal analysis to test the hypothesis that the risk of poor glycaemic control was greater in type 2 DM subjects with severe periodontitis than those who did not have severe periodontitis. Subjects were of at least half Pima ancestry, 18 years or older and reviewed every 2 years. The results suggested that severe periodontitis at baseline had a significant influence on poor glycaemic control at follow-up, after controlling for the other covariates. Similarly, Safkan-Seppälä and Ainamo²⁹ also observed an interrelationship between rapid periodontal breakdown and poor diabetic control.

On the other hand, Hove and Stallard³⁰ found that periodontal breakdown was not related to the severity of DM. In a 9-month longitudinal study on 6 type 1 DM subjects, Sastrowijoto et al³¹ reported that with intensive conventional insulin therapy, long-term metabolic control improved significantly, accompanied by a reduction in gingival redness. However, there was no effect on probing depth, attachment level, bleeding on probing and the plaque index. Thus, improvement in the glycaemic control in type 1 DM patients may not necessarily result in improvement in periodontal parameters, unless local oral hygiene is maintained.

A pilot study carried out on a cohort of patients with diabetes in the local context indicated that individuals with diabetes have more severe periodontal disease than the population at large.³² It was found that 40% of the adult diabetics suffered from moderately advanced periodontal disease as measured by the CPI (Community Periodontal Index) criteria as compared with about 15% in population-based studies.

A recent meta-analysis compared the periodontal status of diabetics with that of non-diabetics.³³ The studies included in the analysis were 18 cross-sectional studies, 3 prospective cohort studies and baseline data of 2 clinical trials. The authors concluded that based on average values, diabetics had poorer oral hygiene as measured by the plaque index, more severe gingival disease as measured by the gingival index, and higher severity of periodontal disease based on probing depths and clinical attachment levels. However, when based on percentages of sites with specific values of the plaque index, the gingival index, bleeding on probing, probing depths, and clinical attachment loss, there was no difference in the extent of disease between the diabetics and non-diabetics.

In summary, there is general agreement that diabetes affects the severity of periodontal disease. While most studies showed that those with poor glycaemic control had more periodontal destruction, not all studies could confirm glycaemic control was significantly correlated to periodontal status indicating that factors other than glycaemic control per se could have contributed to periodontal breakdown. A summary table is illustrated in Table 1.

Clinical Evidence

The clinical evidence that supports a correlation between diabetes and periodontal disease will be reviewed in 3 aspects:

- a) Role of infection on glycaemic control,
- b) Response of patients with diabetes to conventional periodontal therapy, and
- c) Effects of periodontal therapy on glycaemic control.

a) Role of Infection on Glycaemic Control

The interest in the effect of periodontal disease on diabetes may be due to the finding that acute infections alter the endocrinologic-metabolic status, leading to difficulty in controlling blood sugar and increased insulin resistance. Chronic infection may result in poor metabolic control of blood sugar and increased insulin requirements. Rayfield et al³⁴ showed a striking direct correlation between the overall prevalence of infection and the mean plasma glucose levels. There was a significant decrease in intracellular bactericidal activity of leukocytes with *Staphylococcus aureus* and *Escherichia coli* in poorly controlled diabetic subjects when compared with controls. Serum opsonic activity for both *S. aureus* and *E. coli* were significantly lower than that of the control group. Sammalkorpi³⁵ demonstrated that during the acute phase of an infection and the convalescence period, serum insulin increased, with a reduction in plasma glucagon levels. During infection, insulin resistance increased by 33%, whereas during the convalescence period, it increased by 28%, regardless of infective agents. The mechanisms by which infections

result in insulin resistance are not clear. Elevated concentrations of catecholamines, growth hormones, and free fatty acids may result in resistance and changes in cortisol and glucagon concentrations. Endogenous mediators released by macrophages like interleukin-1 (IL-1) increase glucose, insulin and glucagons levels in rats, similar to during infections. The secretion of these factors probably triggered metabolic alterations during infections.

Yki-Jarvinen et al³⁶ investigated the severity, duration and mechanisms of insulin resistance caused by acute infections. It was found that during infection, the glucose requirements in the test patients were 52% less than weight- and age-matched normal subjects. One to 3 months after recovery, the patients' glucose requirements were still significantly lower than matched normal subjects. The authors concluded that acute infections induce severe and long-lasting insulin resistance, which is localised to glucose-utilising pathways. The rate of carbohydrate oxidation is normal during infections, but the rate of non-oxidative glucose disposal is almost zero. The apparent blockade in glucose storage could be due to diminished glycogen synthesis, accelerated glycogenolysis, or both.

Grossi et al³⁷ suggested that chronic gram-negative infections and chronic endotoxemia, like those seen in periodontal disease, resulted in elevated secretion of IL-1 β , tumour necrosis factor- α (TNF- α), interleukin-6 (IL-6), and prostaglandin E₂ (PGE₂). These cytokines could induce insulin resistance and a worsening of metabolic control in diabetic patients. For example, the presence of TNF- α inhibits phosphorylation of insulin receptor substrate-1, resulting in insulin resistance.³⁸

Thus, good control of serum glucose in diabetic patients appears to be a desirable goal in preventing certain infections and to ensure maintenance of normal host defense mechanisms that determine resistance and response to infection.

b) Response of Patients with Diabetes to Conventional Periodontal Therapy

Controlled studies have shown that the response of diabetics to non-surgical and surgical periodontal therapy is similar to that of non-diabetics. A study of 57 young adult type 1 diabetes subjects found no differences from controls for gingival inflammation and plaque index at baseline, and 1 week after scaling and oral hygiene instructions.³⁹ Similar findings were reported by Tervonen and co-workers,⁴⁰ Tervonen and Karjalainen,⁴¹ and Christgau et al.⁴²

In the study conducted by Tervonen and Karjalainen,⁴¹ they studied the variation in periodontal health status and the response to oral hygiene education, scaling and root planing in 36 type 1 DM subjects at 4 weeks, 6 months and 12 months. The subjects were divided into 3 groups based

Table 1. Summary of Periodontal Findings in Individuals with Diabetes

Study	Sample	Population (Age)	Periodontal findings	Effects of glycaemic control
Cohen et al ¹¹	21 DM 18 healthy	(18-35)	DM > gingival score and > LOA	Not discussed
Glavind et al ¹²	51 controlled DM 51 healthy	Type 1 (20-40)	>LOA: DM age 30+ DM of >10 y duration DM with retinal changes No diff between DM & healthy (age, 20-30)	Insulin dosage not related to periodontal destruction
Cianciola et al ¹³	263 DM 208 healthy	Type 1	9.8% of DM had periodontitis vs 1.7% of healthy controls (age, 11 to 18 years) More severe periodontal disease with comparable plaque control	Average duration of DM longer in moderate to severe periodontitis groups
Moore et al ¹⁴	320 DM	Type 1 (Mean 32.1)	Older patients had greater LOA Higher prevalence of periodontal disease associated with -cigarette smoking -older age -later age of DM onset	
Nelson et al ¹⁸	56 DM 645 healthy	Type 2 Pima Indians (15-54)	DM 2.6 times greater incidence of periodontitis	
Emrich et al ¹⁹	254 DM 1088 healthy	Type 2 (15-55)	DM 3 times increased risk of periodontal disease as compared with healthy	
Firatli ²¹	44 DM 20 healthy	Type 1 (Adolescents)	Increased LOA in DM Duration of DM correlated with LOA	
Tervonen & Knuuttila ²³	50 DM 53 controls	(<30->40)	Well-controlled DM better periodontal health	Poorly controlled DM increased attachment loss
Tervonen & Oliver ²⁴	75 DM	Type 1 & 2 (20-70)		Poorer control -increase in periodontitis severity -increase in calculus extent
Guzman et al ²⁵	100 DM	(19-78)	66% of DM had periodontal breakdown Of which 43% had severe periodontal disease	With decreasing DM control, prevalence of LOA increased
Campus et al ²⁶	71 DM 141 healthy	(35-75)	DM -fewer number of teeth -greater number of PD >4 mm -greater percentage of PD >4 mm	DM subjects with good glycaemic control had significantly better periodontal condition than poorly controlled subjects
Engbretson et al ²⁷	45 DM	Type 2 (Mean 54)		Subjects with HbA1c >er 8% → significantly higher mean GCF IL-1 β levels than those <8%
Safkan-Seppälä & Ainamo ²⁹	44 poorly controlled 27 controlled	Type 1 (17-63)		With similar plaque control, those with poor diabetic control had greater LOA and bone loss, compared to the controlled diabetics
Hove & Stallard ³⁰	28 DM 16 controls	(20->40)	DM -more periodontal disease -greater vascular changes	Severity of DM little effect on periodontal breakdown Duration of DM not related to increased breakdown
Sastrowijoto et al ³¹	6 DM	Type 1 (18-50)		Improved glycaemic control -decreased gingival redness -no effect on other periodontal parameters

DM: diabetes mellitus; GCF: gingival crevicular fluid; HbA1c: glycated haemoglobin; IL-1 β : interleukin-1 β ; LOA: loss of attachment; PD: probing depths

on good, moderate and poor metabolic control over the past 3 years, and 10 non-diabetic control subjects were also included. These subjects were not placed on 3-monthly supportive therapy. There were no statistically significant differences in the periodontal status between the diabetic group as a whole and the controls. However, the poorly controlled diabetic group (HbA1c $\geq 10\%$, with diabetic complications), had a significantly greater percentage of sites with attachment loss of greater than 2 mm than the other 2 diabetic groups at baseline. At the 12-month review, the poorly controlled group showed 3 times the number of pockets greater than 4 mm, as compared to other diabetic groups. There were also significantly more sites with subgingival calculus in the same group when compared to the other 2 diabetic groups at 6 months and 12 months. It was observed that poorly controlled diabetics responded similarly to controls in the short term (4 weeks) to non-surgical therapy, but in the absence of maintenance therapy, more rapid recurrence of periodontal pockets and subgingival calculus was found. The increased periodontal breakdown was attributed as a complication of DM. Similarly, DM subjects with severe periodontitis presented with more rapid deterioration without periodontal intervention.⁴³ Based on these findings, information on the level of glycaemic control in diabetic subjects appears to be useful in assessing periodontal prognosis and the need for periodontal therapy on an individual basis.

Westfelt et al⁴⁴ concluded in their study that both diabetic patients and non-diabetics responded similarly to periodontal therapy over a 5-year period with non-surgical and subsequent surgical treatment. This investigation consisted of 20 patients with DM (type 1 and 2) and 20 age- and sex-matched controls with similar periodontal destruction. All patients underwent basic periodontal therapy initially and modified Widman flap surgery at sites with bleeding on probing and probing depth of more than 5 mm, at the 6-month review. During the period of the study, patients were kept on 3-monthly supportive periodontal therapy. It should be noted that in this study, the diabetics were relatively well-controlled metabolically, with the majority of the subjects having HbA1c below 10%. The authors found that individuals with diabetes and non-diabetic controls responded similarly when treated for moderate to advanced periodontitis, and healthy periodontal conditions can be maintained during the 5-year period. This study also showed minimal changes to the HbA1c levels with periodontal therapy. The findings concurred with that of Christgau et al,⁴² who reported no statistically significant differences in healing response to non-surgical periodontal therapy between 20 well-controlled diabetics with HbA1c level of 6.5% (type 1 and 2) and 20 matched controls in a 4-month study period.

In summary, the conclusion drawn from most of the studies indicate that subjects with well-controlled diabetes exhibit clinical healing similar to non-diabetics, at least in the short term. However, due to the small number of subjects in the studies, it could be argued that there may not be adequate power to demonstrate any differences which may exist. On the basis of the available findings, there is no substantial evidence that suggests individuals with diabetes would require more thorough and aggressive periodontal therapy than standard periodontal therapy. However, with poorly controlled diabetics, periodontal health appears to deteriorate more rapidly than in healthy individuals. Therefore, assessment of patients' metabolic status is important in determining the prognosis and recall interval for periodontal therapy.

c) Effects of Periodontal Therapy on Glycaemic Control

One important issue related to periodontal therapy in diabetics is whether the control of periodontal infection improves metabolic control. However, to date, there have been relatively few intervention studies that examine the effect of periodontal therapy on the metabolic status of diabetes.

Periodontal therapy without the use of antimicrobials: Stewart et al⁴⁵ designed a study to investigate the effect of periodontal treatment on glycaemic control in subjects with type 2 DM. The treatment group consisted of 36 patients with type 2 DM who received therapy for adult periodontitis. Treatment included oral hygiene instructions, full mouth scaling, root planing, subgingival curettage under local anaesthesia and extractions of teeth deemed unsalvageable. The control comprised 36 subjects with type 2 DM who did not receive periodontal treatment. The 2 groups were matched for most parameters investigated. During the 9-month observation period, the HbA1c level in the treatment group decreased from 9.5 to 7.6 (17.1%) following the completion of dental treatment. During the same time frame, the value in the control group also decreased from 8.6 to 7.7 (6.7%). Both results were statistically significant. The changes that were statistically significant from the treatment group were subjects receiving oral hypoglycaemics and insulin. The results of this study suggested that following periodontal therapy, there was a marked improvement in glycaemic control in individuals with type 2 DM when compared to the non-treatment control group. It should be noted that the follow-up period was about 9 months, which is comparatively longer than most studies, which average 2 to 3 months. Unlike most studies which showed similar result of improved metabolic control with periodontal therapy, antimicrobials were not used in this study, thus excluding its role in influencing metabolic control. In a very recent study by Kiran and co-

workers,⁴⁶ it was found that even in subjects with good glycaemic control (6% to 8%), a significant improvement in HbA1c was obtained following periodontal therapy.

On the contrary, Westfelt and co-workers⁴⁴ and Christgau et al⁴² found in their respective studies that periodontal therapy did not affect the metabolic status of diabetic subjects. Similarly, Aldridge et al,⁴⁷ and Smith et al⁴⁸ found, from their short-term studies, that although clinical periodontal improvements were significant, there were minimal differences in the mean HbA1c levels.

In summary, although an overall improvement in periodontal health was observed following periodontal therapy, there is no consistent agreement as to the beneficial effects of periodontal treatment on the metabolic control of patients with diabetes. Therefore, the periodontal treatment effect appears to be more important than the systemic factor in determining improvement in periodontal status. Larger scale randomised control trials may be required for adequate statistical power as well, since most studies to date have had subject sizes of less than 30.

Periodontal therapy with the use of antimicrobials: One of the earliest reports was that by Williams and Mahan,⁴⁹ who in a non-controlled case series reported that 7 of 9 patients with diabetes, when treated with extractions, root planing, gingivectomy and antibiotics, showed a significant reduction in blood sugar level and subsequent insulin requirement. The interpretation of results should be carefully considered as there was no statistical analysis and the measurements of metabolic control were crude by present standards. The study, however, did suggest that controlling oral infection like periodontitis could improve the metabolic control of diabetes.

Miller et al⁵⁰ carried out a pilot study to evaluate the effects of controlling gingival inflammation on blood glucose levels as determined by glycosylation of haemoglobin and albumin, in poorly controlled diabetic patients with periodontitis. The study had 9 subjects, with a follow-up period of 8 weeks after periodontal therapy. Doxycycline and chlorhexidine mouthrinse were prescribed together with basic periodontal therapy. There was an improvement in average glycated haemoglobin value in the 5 subjects who responded well to the periodontal therapy. Glycated albumin value showed some improvement, which was more variable. The authors thus concluded that periodontal therapy for uncontrolled diabetics may reduce their insulin requirement and improve their metabolic control. However, the results should be interpreted with caution, as the review period of 2 months may not be adequate in detecting changes in HbA1c value, since it measures the glycaemic control over 2 to 3 months. The study is also a cohort study with no control group.

Grossi and co-workers⁵¹ studied the effects of periodontal treatment on the level of diabetic metabolic control of 113 Pima Indians suffering from both type 2 DM and periodontal disease. All groups showed clinical and microbial improvement, with the doxycycline-treated groups showing the greatest probing depth reduction and subgingival *Porphyromonas gingivalis* reduction, as compared to the control. In the 3 groups receiving systemic doxycycline, there were significant reductions in mean glycated haemoglobin levels by 10% from pretreatment levels, at 3 months. At 6 months, values were comparable to baseline. This study thus concluded that effective treatment of periodontal infection and reduction of periodontal inflammation were associated with a reduction in the level of glycated haemoglobin, in the short term. It should be noted that doxycycline, which has antimicrobial and anti-collagenase activity, may be the reason for the improved results rather than periodontal therapy per se.

On the other hand, a more recent clinical trial by Rodrigues and co-workers⁵² failed to show any additional benefit of adjunctive antibiotics. HbA1c levels were significantly reduced in the scaling and root planing alone group, while the group with periodontal therapy and antibiotics showed no significant differences. The improvement in HbA1c levels for both groups was statistically different. This study concluded that periodontal treatment alone without antibiotics could also result in improved periodontal status as well as glycaemic control of the study population. It should be cautioned that the sample size was small, with only a short follow-up of 3 months. Though the subjects were randomly divided into either treatment groups, the group given antibiotics, had more diabetic complications and initial fasting glucose levels. This may have some bearing on the treatment response.

It is hypothesised that successful periodontal therapy appears to reduce circulating TNF- α levels significantly in both systemically healthy periodontitis patients⁵³ and diabetic patients.⁵⁴ Iwamoto et al⁵⁴ examined the periodontal and diabetic status of 13 type 2 diabetes patients. Patients were treated with local delivery minocycline in all periodontal pockets once a week for a month. The number of total bacteria in the periodontal pockets, circulating TNF- α levels and HbA1c value were assessed before and after treatment. They hypothesised that TNF- α produced due to periodontal inflammation synergistically affects insulin resistance as well as TNF- α produced from adipose tissues in insulin-resistant type 2 diabetes patients. With antimicrobial periodontal therapy, there was significant reduction in the number of microorganisms in periodontal pockets, circulating TNF- α levels and HbA1c value. Six subjects not receiving insulin therapy demonstrated decreased fasting insulin levels. The average reduction in

circulating TNF- α levels and HbA1c value were 0.49 pg/ml and 0.8% respectively. Thus it is concluded that antimicrobial periodontal therapy is effective in improving metabolic control in diabetics, possibly through reduced serum TNF- α and improved insulin resistance. The authors also suggested that increased TNF- α caused by chronic inflammation may have an additive effect on insulin resistance in type 2 diabetes patients, thus controlling periodontal infection plays an important role in the overall management of these patients. A recent study by Martorelli de Lima and co-workers⁵⁵ demonstrated that the adjunctive use of locally delivered doxycycline improved the periodontal attachment levels of diabetic patients with periodontitis as compared with controls who received scaling and root planing. Similar results were shown with adjunctive systemic doxycycline, in addition to non-surgical periodontal therapy.⁵⁶

In summary, there is no definite conclusion as to whether periodontal therapy per se affects the glycaemic control of patients with diabetes. A summary table can be found in Table 2.

Factors which may influence the treatment outcome could be related to metabolic control, oral hygiene status, and the degree of periodontal destruction. It appears that antibiotic, used as an adjunct to periodontal therapy, does offer an added advantage in controlling infections, as well as decreasing HbA1c levels.

Pathogenic Mechanisms

The Relationship between Diabetes and Periodontal Disease: Biological Basis

Periodontal disease includes both gingivitis and periodontitis. Gingivitis is defined as the condition where inflamed gingival tissues are associated with a tooth with no attachment loss or with previous attachment and bone loss (reduced periodontal support), but is not currently losing attachment or bone. Periodontitis, on the other hand, is defined as an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both. It is a multifactorial disease. The development of periodontitis is dependent on many factors, like the microbial challenge, genetic risk factors, environmental and acquired risk factors.

Cellular response: Polymorphonuclear leukocyte (PMN) is important in the maintenance of gingival and periodontal health. They are the first line of a host's defense mechanism in the inflammatory process. They are primarily protective against periopathogenic bacteria and play a role in periodontal wound healing. However, there is impaired PMN function in patients with diabetes. The diabetic state

thus decreases host-resistance to infection via defects in polymorphonuclear leukocyte functions like chemotaxis, phagocytosis, intracellular bactericidal activity and serum opsonic activity. The possible explanation for the increase in prevalence and severity of periodontal disease in diabetes could be due to the reduced polymorphonuclear leukocyte chemotaxis and phagocytosis defects, and a depressed humoral response, thus reducing the diabetic patients' ability to combat infection, including periodontal infection. This depressed immune response may explain why it may not be possible to eradicate periodontal infection totally in diabetics after conventional periodontal therapy. Thus, a few authors, like Smith et al,⁴⁸ have commented that conventional mechanical therapy of scaling and root planing in moderate to deep pockets and good oral hygiene in diabetic patients may be inadequate in maintaining the periodontium in a stable state. The clinical improvements of such therapy may be short term and adjunctive therapy may be needed to help control the periodontal infection. This may be one of the reasons why antibiotics may be indicated with mechanical therapy for diabetic patients, especially for uncontrolled cases.

Alpagot et al⁵⁷ suggested that gingival crevicular fluid neutrophil elastase activity, age and smoking are risk indicators for periodontal disease in diabetic patients. In this study, periodontal disease was not associated with the duration and metabolic control of diabetes. Thus, impaired neutrophil function, rather than the control of glucose abnormalities, predisposes diabetic patients to the development of periodontitis. Elastase is usually released by neutrophils to the gingival crevice as a result of host-microbial interactions. Elevated elastase in crevicular fluid has been associated with periodontal disease in non-diabetic subjects. Other evidence include an increase in the release of the enzyme β -glucuronidase, a lysosomal enzyme released during the inflammatory process by the degranulation of PMNs.⁵⁸

Effects of hyperglycaemia: In a hyperglycaemic environment, numerous proteins including collagen undergo a non-enzymatic glycosylation process to form advanced glycation end-products (AGE). AGE formation changes the function of numerous extracellular matrix components, affecting collagen stability and vascular integrity. AGE formation on collagen causes increased cross-linking between collagen molecules, resulting in reduced solubility and decreased turnover rate. Monocytes, macrophages and endothelial cells possess high-affinity receptors for AGEs. Binding of AGE to macrophage and monocyte receptors result in a hyper-responsive cellular state, resulting in increased secretion of IL-1, insulin-like growth factor and TNF- α , while endothelial cell binding results in focal thrombosis and vasoconstriction. Diabetic patients with

Table 2. Summary of Studies Examining the Effects of Periodontal Therapy on Glycaemic Control

Study	Study type	Study period (months)	Sample	Diabetes type	HbA1c	Antibiotics	Results
Aldridge et al ⁴⁷	RCT	2	16 T vs 15 C	Type 1	9.5%	No	No difference in HbA1c
Smith et al ⁴⁸	Case-controlled study	2	18 T vs 18 healthy C	Type 1	8.18%	No	No difference in HbA1c
Westfelt et al ⁴⁴	Case-controlled study	60	20 T vs 20 healthy C	Type 1 & 2		No	No difference in HbA1c
Grossi et al ⁵¹	Case-controlled study	3,6	113	Type 2	9.2%-10.7%	Yes Doxycycline	At 3 months – 10% decrease in HbA1c At 6 months, no difference
Christgau et al ⁴²	Case-controlled study	4	20 T vs 20 healthy C	Type 1 & 2	6.5%	No	No difference in HbA1c
Promsudthi et al ⁴³	RCT	3	27 Tx vs 25 no Tx	Type 2	7.5%-11%	No	No difference in HbA1c value. Sig improvement in periodontal status Increase LOA with no treatment
Williams and Mahan ⁴⁹	Cohort study	3	9	Type 1	-	Yes Penicillin, streptomycin	Reduced insulin requirement
Miller et al ⁵⁰	Cohort study	2	9	Type 1	9.44%	Yes Doxycycline (systemic)	Reduction of HbA1c to 9.01% with therapy Gp with improvement of periodontal status, HbA1c 8.7% → 7.8%
Iwamoto et al ⁵⁴	Cohort study	1	13	Type 2	7.9%	Yes Minocycline (local)	HbA1c improved significantly by 0.8%
Stewart et al ⁴⁵	Case-controlled study	9	36 T vs 36 C	Type 2	T-9.2% C-8.5%	No	Test gp sig improvement in HbA1c by 17%
Rodrigues et al ⁵²	RCT	3	15 AB vs 15 without AB	Type 2	AB 9.5% No AB 8.8%	Yes Amoxycillin/clavulanic acid 875 mg	Periodontal therapy alone with no AB, HbA1c sig improvement
Kiran et al ⁴⁶	RCT	3	22 Tx vs 22 no Tx	Type 2	6%-8%	No	Sig improvement in periodontal parameters and HbA1c in test gp by 10%

AB: antibiotic; BOP: bleeding on probing; C: controls; Gp: group; HbA1c: glycated haemoglobin; LOA: loss of attachment; PD: probing depths; RCT: randomised controlled trial; Sig: significantly; T: test; Tx: treatment

periodontitis have significantly higher gingival crevicular fluid levels of IL-1 β and PGE₂ than non-diabetics. The AGE-mediated events are of primary importance in the pathogenesis of diabetic complications. They may be involved in tissue changes within the periodontium, and patients with poor glycaemic control and elevated AGE levels may therefore be more susceptible to increased tissue destruction.

Hyperglycaemia also causes thickening of vascular basement membranes thus reducing tissue nutrition and migration of leukocytes. The maturation and homeostasis of collagen appear to be affected by glucose levels. Gingival

fibroblasts from diabetic patients synthesise less collagen compared to non-diabetic subjects. Collagenase activity is increased in the gingival tissue of diabetic patients as well. This could partly explain why patients given doxycycline showed improved periodontal healing.

Therefore, long-standing DM and poor metabolic control result in microvascular and neurological changes, impairment of collagen synthesis and diminished function of polymorphonuclear leukocytes.

Microbiological response: The bacteria involved in periodontitis are usually anaerobic Gram-negative bacteria. The pathogenic effect of Gram-negative bacteria which

causes direct and indirect damage to the periodontal supporting tissues via its toxic products and activation of a series of inflammatory reactions, is well documented.⁵⁹ Gram-negative bacteria-derived lipopolysaccharide (LPS) is also considered a potent inducer of TNF- α from monocytes and macrophages. LPS are endotoxins present in the bacterial cell walls of periodontal pathogens. Lang et al⁶⁰ and Ling et al⁶¹ found that infusion of bacterial LPS, which is a potent inducer of TNF- α , resulted in severe insulin resistance in rat models. Therefore, periodontal disease may exacerbate insulin resistance in diabetic patients.

Several studies have been conducted to examine the microflora of patients with DM. However, results have been rather inconsistent. Mashimo et al⁶² found that in type 1 DM patients, *Capnocytophaga species* and anaerobic vibrios seemed to be predominant. This may contribute to an increase in periodontal diseases. Conflicting results were reported by Sastrowijoto and co-workers.⁶³ They found high levels of *Porphyromonas gingivalis*, *Prevotella intermedia* and *Actinobacillus actinomycetemcomitans*, with low levels of *Capnocytophaga species*, in periodontal pockets of patients with type 1 DM. However, *streptococci* which is associated with periodontal health was shown to increase with improvement in glycaemic control.⁶⁴ In another study comparing patients with type 1 DM and their non-DM healthy siblings staying together, Sbordone and co-workers⁶⁵ found no difference in their levels of *Porphyromonas gingivalis*, *Prevotella intermedia*, *Actinobacillus actinomycetemcomitans*, and *Capnocytophaga species*. Similarly, Tervonen and co-workers⁶⁶ found no significant relationship between the prevalence of periodontopathogens and diabetic factors in diabetic patients with relatively good metabolic control and early periodontitis. It is likely that other factors may be more important in the increased prevalence and severity of periodontal diseases in the poorly controlled diabetics.

Role of TNF- α : Several studies have reported TNF- α to be a strong candidate responsible for insulin resistance. In a normal situation, when insulin binds to the insulin receptor on muscle and fat cells, a tyrosine residue of cytoplasmic domain of the insulin receptor is autophosphorylated. A signal is transduced and translocated to the cell membrane to take up glucose. However, in the presence of TNF- α , this process is inhibited, thus influencing glucose uptake by cells resulting in insulin resistance.^{38,67,68} The possible role of periodontal disease on diabetes control is outlined in Figure 1.

Salvi et al⁶⁹ reported that diabetics as a group had a significantly higher monocytic TNF- α production in response to increasing *Porphyromonas gingivalis* LPS concentrations as compared to non-diabetics with gingivitis or adult periodontitis. Forty per cent of type 1 diabetes patients with periodontitis demonstrated a 62-fold increase

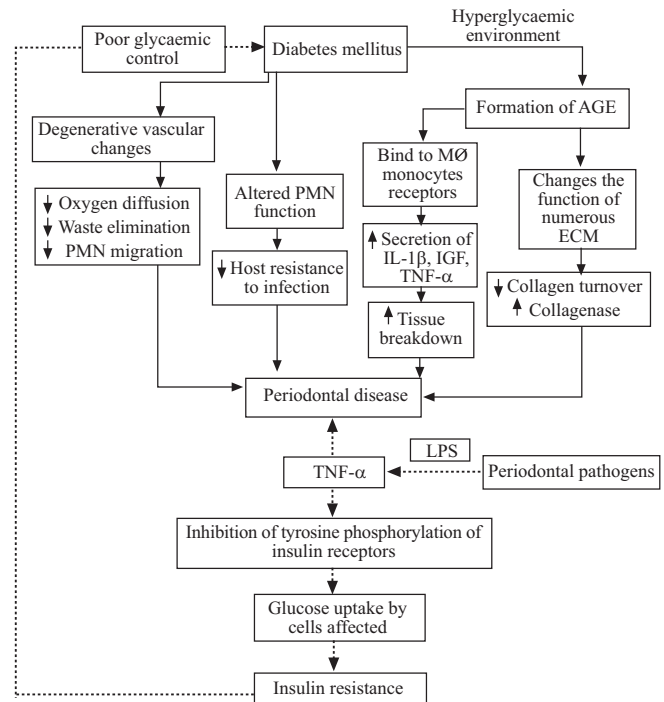


Fig. 1. Proposed pathogenesis of periodontal disease in diabetes.

AGE: Advanced glycated end-products

ECM: Extracellular matrix

IGF: Insulin-like growth factor

IL-1 β : Interleukin-1 β

LPS: Lipopolysaccharide

MØ: Macrophages

PMN: Polymorphonuclear leukocytes

TNF- α : Tumour necrosis factor- α

↓: Decreased

↑: Increased

in TNF- α secretion when compared with non-diabetic patients with gingivitis or periodontitis, and a 13.5-fold increase in comparison with type 1 diabetes subjects with gingivitis or mild periodontitis.

The possible mechanism explaining periodontal breakdown in diabetes is outlined in Figure 1. In summary, the increased risk to periodontal disease in diabetes is triggered by the plaque biofilm and the hyperglycaemic state, both of which result in a series of synergistic inflammatory reactions, with release of inflammatory mediators and cytokines causing tissue destruction and an impairment in healing responses.

Conclusions and Future Directions

Upon reviewing the available evidence, the following conclusions could be made:

1. Diabetes is associated with more severe periodontal breakdown in cross-sectional and longitudinal studies.
2. The extent of periodontal destruction in diabetes is influenced directly or indirectly by glycaemic control and the individual immuno-regulatory capacity.

3. The response of well-controlled diabetes to non-surgical periodontal therapy is comparable with that of non-diabetic controls.
4. Periodontal therapy may or may not have a direct impact on glycaemic control.
5. There is still no clearly defined evidence as to whether treatment of periodontal infection contributes to the management of glycaemic control in both type 1 and type 2 diabetes.

The inconsistencies in the results may be related to the methodology in the study design, and differing criteria for diagnosing diabetes and assessing the level of glycaemic control. Some studies concentrated on type 1, some on type 2 DM, some both type 1 and 2 subjects. The subjects had varied levels of glycaemic control: some were well-controlled while others were poorly controlled. Different parameters were also used to monitor glycaemic control, like HbA1c values (most popular), fructosamine levels, or serum glucose levels. The follow-up periods were also not consistent, ranging from 2 months to 5 years or more. Therefore, further long-term studies are needed to prove that periodontal treatment can improve metabolic control of diabetes by reducing glycated haemoglobin levels. Studies examining the role of periodontal therapy on metabolic control in both types of DM should utilise a randomised prospective design with a large sample size for adequate power. The studies should examine the effect of periodontal disease severity on glycaemic control, the degree of healing needed to affect glycaemic control, the duration of the effect and interval for metabolic monitoring after periodontal therapy, and any differences in response observed in type 1 and 2 DM.

If it is true that AGE and TNF- α play a key role in periodontitis-induced insulin resistance, studies to examine what type of periodontal therapy reduces circulating glycated end-products and TNF- α levels will be useful. Studies to examine whether blocking TNF- α with neutralising antibodies is effective in improving insulin resistance without conventional periodontal therapy will also be of interest. In view of the increased risk to cardiovascular problems in diabetes, the role of other potential risk markers such as C-reactive proteins and cholesterol on periodontal disease severity should also be explored. More studies to examine the association of IL-1 genotype and subjects with diabetes and periodontal disease may also be useful in establishing the possible risk factors for this group of subjects.

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