ASSOCIATION OF PERIODONTITIS WITH DIABETES MELLITUS : A REVIEW

Gaurav Malik, Gurvanit Lehl, Manjit Talwar

Department of Dentistry, Govt. Medical College and Hospital, Chandigarh.

ABSTRACT

The association between diabetes mellitus and periodontitis has long been discussed with conflicting conclusions. Both of these diseases have a relatively high incidence globally in the general population with a number of common pathways in their pathogenesis. Diabetis mellitus and Periodontitis are polygenic disorders with some degree of immuno-regulatory dysfunction. Numerous reports indicate a higher incidence of periodontitis in diabetics compared to healthy controls. The relationship between these two maladies appears bi-directional insofar that the presence of one condition tends to promote the other, and that the meticulous management of either may assist treatment of the other. However, the *converse possibility* that periodontal disease either predisposes or exacerbates the diabetic condition has received little attention This review attempts to explain the immunobiological connection between periodontal disease and diabetes mellitus, exploring the mechanisms through which periodontal infection can contribute to the low-grade general inflammation associated with diabetes (thus aggravating insulin resistance) and discussing the impact of periodontal treatment on glycemic control in people living with both diabetes and periodontal disease. A PubMed and a general internet search were carried out to identify the relevant indexed scientific publications, specifically addressing the association of diabetes mellitus (DM) with periodontitis (PD). Publications focusing on the mechanisms through which periodontal infections contribute to the diabetes-related inflammatory state, the influence of periodontal infections on insulin resistance and the ways in which treatment of these infections can influence glycemic control were reviewed.

Key words: Periodontitis, type 2 diabetes mellitus, glycemic control, insulin resistance, periodontal therapy.

INTRODUCTION

Most of the connective tissue destruction-taking place in periodontal disease results from the interaction of bacteria and their products with mononuclear cells.[1] One possible mechanism to explain as to why diabetics have more severe periodontal disease is that glucose mediated AGE(advanced glycation end products) accumulation would affect migration and phagocytic activity of mononuclear and polymorphonuclear phagocytic cells resulting in establishment of more pathogenic sub-gingival flora. This triggers an infection-mediated pathway of cytokine regulation, especially with secretion of TNF-α and IL-1 and a state of insulin resistance, affecting glucose utilizing pathways. Excessive local secretion of TNF-α and IL-1 also mediates tissue destruction of connective tissue and alveolar bone evident in periodontal disease. Monocytes in diabetic individuals may be primed by age protein binding. Periodontal infection challenge to their perceived phagocytic cell may in turn amplify the magnitude of the macrophage response to age protein, enhancing cytokine production and oxidative stress. Simultaneously periodontal infection may induce a chronic state of insulin resistance, contributing to the cycle of hyperglycaemia, non-enzymatic irreversible glycation. Age protein binding and accumulation thus amplifying the classical pathway of diabetic connective tissue degradation, destruction and proliferation, which is AGE-mediated. Hence a study proposed that periodontal infection mediated cytokine synthesis and secretion may amplify the magnitude of the AGE mediated cytokine response and vice versa.[2] In doing so and in a manner similar to other bacterial infection, the relationship between diabetes mellitus and periodontal infection becomes two way. This dual mechanism of tissue destruction suggests that control of periodontal infection is essential to achieve long term control of diabetes mellitus (Fig.1).[2]

Corresponding Author :

Dr. Gaurav Malik,
1010/1, Sector 39B, Chandigarh
Email- malik.911@gmail.com

Influence of Periodontitis on Diabetes

Evidence has consistently indicated that diabetes is a risk factor for increased severity of gingivitis and

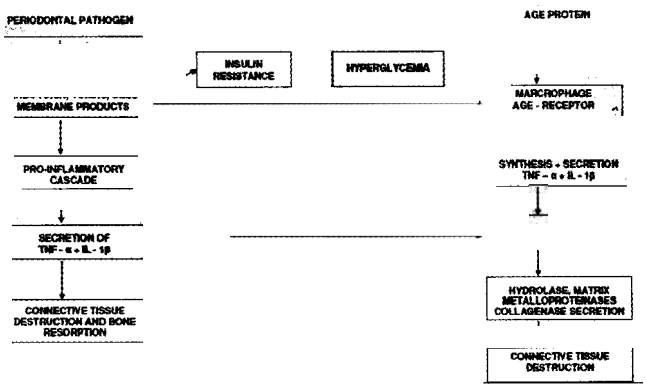

Fig. 1 : Proposed Model : Two Way Relationship Between Diabetes And Periodontics

periodontitis.[3] Conversely, periodontitis may be a risk factor for worsening glycemic control among patients with diabetes and may increase the risk of diabetic complications. Periodontitis may initiate or propagate insulin resistance in a manner similar to that of obesity, by enhancing activation of the overall systemic immune response initiated by cytokines.[3,4] Given these mechanisms promoting insulin resistance, it seems that in individuals with type 2 diabetes and periodontitis, an elevated chronic systemic inflammatory state induced by periodontal disease may contribute to insulin resistance through a "feed-forward" mechanism, worsening glycemic control[4]. This might explain why periodontitis increases the risk of poor glycemic control among patients with type 2 diabetes. Periodontitis may also contribute to the elevation of serum inflammatory mediators through enhanced in-vitro production of Tumour Necrosis Factor (TNF-a), Interleukin (IL-1b) and Prostaglandin (PGE_2) by monocytes, as has been shown in patients with both diabetes and periodontitis. This may indicate an innate hyper-responsiveness of these monocytes to periodontal bacterial challenge.[5,6] Periodontitis may also play a role through the translocation of gram-negative species and their products from the periodontal biofilm into the circulation and through direct cytokinemia from the gingival crevicular fluid (i.e., translocation of cytokines from the periodontal space into the circulation).[6] With regard to the last of these mechanisms, poorer glycemic control was associated with increased levels of cytokines, especially IL-1a, in the gingival crevicular fluid.[7] In individuals with type 2 diabetes and periodontitis, serum levels of TNF-a were significantly correlated with the severity of periodontal destruction, plasma endotoxin and IL-1b levels in the gingival crevicular fluid, but not with body mass index (BMI), serum glucose and haemoglobin A_{1c} (HbA_{1c}) levels. Furthermore, there was a dose–response relationship between the severity of periodontitis and serum TNF-a level, which suggested that periodontal disease may play a major role in elevating levels of this cytokine, which is closely linked to insulin resistance.[6] An examination of NHANES III data from participants without diabetes revealed a positive association between BMI and clinical attachment loss. Moreover, those in the highest quartile of body mass (BMI e" 30.8 kg/m^2) had significantly higher serum levels of TNF-a and soluble TNF-a receptors than those in the lowest quartile of body mass (BMI < 24.6 kg/m^2). These data suggest that obesity is associated with both systemic inflammation and periodontal disease and that insulin resistance may mediate this relationship.[8]

Various other studies in the literature have shed light on the effect of periodontitis on diabetes. Because of the high vascularity of the inflamed periodontium, this inflamed tissue may serve as an endocrine-like source for TNF-a and other inflammatory mediators.[2,9] Because of the predominance of gram-negative anaerobic bacteria in periodontal infection, the ulcerated pocket epithelium is thought to constitute a chronic source of systemic challenge from bacteria, bacterial products and locally produced inflammatory mediators. All mediators like TNF-a, IL6, and IL1, are important in periodontal inflammation and have been shown to have effects on glucose and lipid metabolism, particularly following an acute infectious challenge or trauma.[2,10,11] TNF-a has been reported to interfere with lipid metabolism and to be an insulin antagonist.[12,13] IL6 and IL1 have also been reported to antagonize insulin action.[11,14]

Periodontal *Treatment* effecting Systemic Inflammatory State and Glycemic Control

More direct, empirical evidence regarding the effects of periodontal infection on glycemic control of diabetes comes from treatment studies using non-surgical periodontal therapy and observational studies. The treatment studies are a heterogeneous set of reports that include randomized controlled trials (RCTs) and non-randomized controlled trials. The randomized controlled trials used control groups that were either non-treated controls,[15,16] positive controls,[17,18,19] or controls advised to continue with their usual source of dental care.[20] Of the seven randomized controlled trials, four reported a beneficial effect for periodontal therapy.[16,17,18,19]

An important source of variation in the randomized controlled trials is the use of adjunctive antibiotics with

the non-surgical periodontal therapy. Among the randomized controlled trials, four included adjunctive antibiotic use systemically [17,18,20] or locally delivered.[19] Three of these four randomized controlled trials using antibiotic showed beneficial effects on glycemic control.[17,18,19] Hence, to date there is no clear evidence to support a requirement for the use of antibiotics in combination with non-surgical periodontal treatment in order to observe an improvement in glycemic control associated with periodontal therapy.

Among the set of periodontal treatment studies reviewed that were not randomized controlled trials, three reported a beneficial effect on glycemic control [21,22,23] and one did not.[24] Only two of these studies had control or comparison groups.[24,25] Like the randomized controlled trials there was marked variation in the use of adjunctive antibiotics, with three of the five studies that used systemic antibiotics reporting a beneficial effect on glycemic control.[21]

There is marked heterogeneity in the design of the studies, methodology, length of follow-up, types of participants, and periodontal treatment protocols. The details of the variation in this body of literature have been extensively described in several detailed reviews.[2,26,27]

Additional evidence to support the effect of severe periodontitis on increased risk for poorer glycemic control comes from two longitudinal observational studies. A longitudinal epidemiological study conducted in Pima Indians in Arizona, USA [27] found subjects with type 2 diabetes with good to moderate control having severe periodontitis at baseline, to be six times more likely to have poor glycemic control at 2-years follow-up compared to those without severe periodontitis at baseline. In another observational study of 25 adults with type 2 diabetes, aged 58–77 years,[28] also reported an association between advanced periodontal disease and impaired metabolic control.

It is well recognized that poor glycemic control is a major determinant for the development of the chronic complications of diabetes. Results from the landmark Diabetes Control and Complications Trial (type 1 diabetes) and the UK Prospective Diabetes Study (UKPDS) (type 2 diabetes) demonstrated that attaining and maintaining good glycemic control could reduce the risk for and slow the progression of microvascular complications in patients with type 1 and type 2 diabetes(Diabetes Control and Complications Trial Research Group, 1993). Additionally, the UKPDS observed a 16% reduction (P = 0.052) in the risk of combined fatal or nonfatal myocardial infarction and sudden death. Further epidemiological analysis from the UKPDS showed a continuous association between the risk of cardiovascular complications and glycaemia. Every percentage point decrease in HbAlc (e.g., 9–8%), was associated with 25% reduction in diabetes-related deaths, 7% reduction in all-cause mortality and 18% reduction in combined fatal and nonfatal myocardial infarction.

There is emerging evidence from observational studies regarding the association between periodontal disease and the risk for diabetic complications. In a study carried out in Jönköping, Sweden, 39 case-control pairs of individuals with type 1 and type 2 diabetes for 6 years were followed-up. The observation of the study indicated that in each pair of case controls the cases had severe alveolar bone loss and controls had gingivitis or minor alveolar bone loss. They found that cases were significantly more likely to have prevalent proteinuria, and cardiovascular complications including stroke, transient ischemic attacks, angina, myocardial infarction, and intermittent claudication than controls at their follow-up medical assessments.

Two reports from the on-going longitudinal study of diabetes and its complications in the Gila River Indian Community in Arizona, USA, conducted by the National Institute of Diabetes and Digestive and Kidney Diseases, address nephropathy and cardiovascular disease. In a study of a cohort of 628 individuals for a median follow-up time of 11 years, individuals with severe periodontal disease had 3.2 times greater risk for cardio-renal mortality (i.e., ischemic heart disease and diabetic nephropathy combined) than those with no, mild or moderate periodontal disease. This estimate of significantly greater risk persisted while controlling for several major risk factors of cardio-renal mortality including: age, sex, diabetes duration, HbA1c, body mass index (BMI), hypertension, blood glucose, cholesterol, electrocardiographic abnormalities, macroalbuminuria and smoking.[30]

Another report investigated the effect of periodontitis on risk for development of overt nephropathy (macroalbuminuria) and end-stage renal disease (ESRD) in a group of 529 Gila River Indian Community adults with type 2 diabetes. Their proportional hazards model analysis was adjusted for age, sex, diabetes duration, body mass index, and smoking. It indicated periodontitis and edentulism were significantly associated with the risk of overt nephropathy and end-stage renal disease. The

report reviewed incidence of macroalbuminuria and end stage renal disease in individuals with moderate periodontitis, severe periodontitis and in edentulous individuals (with no teeth). The observation of this report showed that macroalbuminuria and end stage renal disease were manifold greater in above groups as compared to those with none/mild periodontitis.[31]

Studies of patients with both diabetes and periodontitis have shown that nonsurgical periodontal therapy with adjunctive local delivery of minocycline reduced circulating levels of TNF-a.[21,32] In one of those studies, the reduction in serum levels of TNF-a was accompanied by and strongly correlated with, a significant decrease in mean HbA_{1c} values (from 8% to 7.1%).[21] Conversely, a pilot study showed that serum levels of TNF-a were not significantly affected 4 weeks after mechanical periodontal therapy.[33] In the same study, systemic levels of mediators such as C-Reactive Protein (CRP) and soluble E-selectin were significantly reduced following nonsurgical periodontal debridement.[33]

Outcomes of a meta-analysis of 10 intervention trials involving 456 patients with diabetes (type 1 or type 2) showed that following mechanical periodontal debridement, HbA_{1c} levels decreased by an average of 0.38% over, all included studies, by 0.66% among patients with type 2 diabetes and by 0.71% among cases in which antibiotics were administered. However, none of these changes were statistically significant.[26] A single-blind, randomized controlled trial confirmed the results of the meta-analysis, showing that periodontal therapy combined with diabetes medication had no statistically significant effect on levels of HbA_{1c} relative to no treatment.[20] Other studies have shown significant improvements in glycemic control with periodontal therapy.[16,22] These conflicting data are difficult to interpret because of the wide range of medical treatment regimens used in study populations, inadequate sample sizes, combined enrolment of patients with type 1 and type 2 diabetes, confounding by smoking and BMI, and study design (e.g., studies examining only short-term outcomes or pilot studies). Although the 0.7% improvement in HbA_{1c} levels attributed to mechanical periodontal debridement and antibiotic therapy reported in the meta-analysis was not statistically significant, its clinical significance should not be minimized, given that the less potent class of oral glucose-lowering agents, the a-glucosidase inhibitors, reduces HbA_{1c} level by 0.5% to 1%.[34] Other classes of oral agents, such as insulin secretagogues, biguanides and thiazolidinediones, as well as nutritional therapy and physical activity, improve glycemic control to a similar degree, with 1% to 2% reduction in HbA_{1c}.[34] Therefore, since periodontal treatment appears to have the same power to lower HbA_{1c} as other glucose-lowering therapies, it may represent an alternative or adjunctive therapy for improving insulin sensitivity and glycemic control in patients with both type 2 diabetes and periodontitis.

SUMMARY AND CONCLUSION

Evidence is emerging to suggest that periodontal disease is associated with increased risk for diabetes complications. Because periodontal diseases are "silent" in nature, most patients do not realize they have such conditions until significant destruction has occurred. Likewise, physicians may not know that their patients have a condition that could alter glycemic control and make diabetes management more difficult. It is important for clinicians to discuss with their diabetic patients the increased risk for periodontal diseases. Treating periodontal infection in people with diabetes is clearly an important component in maintaining oral health. It may also have an important role in establishing and maintaining glycemic control and possibly in delaying the onset or progression of diabetic complications. Systematic study in diverse populations is warranted to support existing evidence that treating periodontal infections can contribute to glycemic control management and possibly to the reduction of the burden of complications of diabetes mellitus. Awareness, attitudes and orientation of health care providers both dentist and physicians are essential in better health outcomes for the patient. An inter disciplinary approach in health care is the need of the hour. More research to better understand the level of awareness, attitudes and orientations of health-care providers (both dentists and physicians), and even patients themselves, when it comes to diabetes and its relationship with periodontal diseases, is warranted. There is clearly room for improvement in clinical practice, and looking ahead, research towards developing clinical support systems for dentists (and dental hygienists, physicians, nurses, diabetes educators, dieticians) and also programmes that facilitate the interaction and synergy among all health-care providers involved in the care of diabetic individuals is of essence.

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