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Diabetes mellitus and periodontal diseases: A two way relationship

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Abstract

Diabetes mellitus and periodontits are both highly prevalent chronic inflammatory diseases. Both diseases share the same risk factors and are a significant global health care burden adversely affecting the quality of life. Evidence from various studies have demonstrated that diabetes is a major risk factor for periodontal disease and is associated with increased incidence, prevalence and severity of periodontal disease. Hyperglycemia associated with diabetes mellitus results in an increased host immunoinflammatory response which adversely affects the periodontal health. Conversely, periodontits is associated with poor metabolic control in patients with diabetes and increased development of diabetic complications suggesting a bidirectional relationship between the two diseases. Periodontal infection via bacteremia exerts a wide systemic effect by contributing to chronic systemic inflammatory burden worsening diabetic state by increasing insulin resistance. Moreover, studies have demonstrated an improvement in glycemic control following periodontal therapy in prediabetic and diabetic patients with periodontitis.

Keywords: Risk factors, Diabetes mellitus, Hyperglycemia, Periodontal disease, Periodontitis.

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INTRODUCTION

Chronic systemic diseases, including cardiovascular diseases, cancer, diabetes and chronic respiratory diseases are the leading cause of death globally accounting for 71% of all deaths worldwide and represent a significant global burden of diseases.[1] Inflammatory periodontal diseases (gingivitis and periodontitis) are highly prevalent oral conditions that affect the supporting tissues of the teeth[2,3] and are closely linked to other noncommunicable diseases (NCDs) and disorders (e.g., diabetes, cardiovascular disease, pulmonary diseases, rheumatoid arthritis, kidney disease and cognitive impairment) via multiple plausible mechanisms and pathways of infection (e.g. bacteremia), inflammation, dysbiosis and common risk factors.[4,5]

Of the various chronic systemic diseases that have been linked to periodontal diseases, the association between periodontal diseases and diabetes mellitus (DM) has been studied extensively and is the most consistent.[6]

In all the studies linked to these two pathologies, periodontal diseases is regarded as having a bidirectional relationship with diabetes mellitus as diabetes adversely affect periodontal health and severe form of periodontal diseases is associated with adverse outcome in diabetic patient.[7-12]

Periodontal diseases and DM are both complex,multifactorial,chronic,and inflammation-based diseases, often occur in the same individuals and share common risk factors like higher age, male gender, minority race/ethnicity, low socioeconomic status, genetic predisposition, smoking, excessive alcohol consumption, unhealthy diet, obesity, physical inactivity, and stress.[13-15]

This article reviews the literature regarding the association between periodontal diseases and diabetes mellitus.

PERIODONTAL DISEASES

Periodontal diseases consist of a range of inherited or acquired chronic inflammatory conditions that affect the supporting tissues of the teeth.[16,17]

Gingivitis and periodontitis are the two main forms of the periodontal diseases which occur by a complex interaction between dysbiotic periodontal microbiome and host immune response and this interaction is

influenced by various environmental and genetic factors that alter the immuno-inflammatory response of the host.[17-19] The global prevalence of periodontal disease is about 20-50 %.[20]

Gingivitis is a localized inflammation of the gingiva initiated by bacteria in the dental plaque and is reversible with plaque control measures but if left untreated can progress to periodontitis in susceptible individuals.[12,17]

Periodontitis is a chronic inflammatory disease induced by dysbiotic microbiota that leads to the destruction in the periodontium of susceptible individuals.[21,22] It is a multifactorial disease that results from complex interactions between the dysbiotic microbiota, the inflammatory immune response, genetic factors, epigenetic influences and harmful environmental exposure.[23,24] Clinical features of periodontitis include gingival bleeding, formation of a periodontal pocket between the gingiva and the tooth, clinical attachment loss and radiographically assessed alveolar bone loss.[21]

In clinical practice a patient is a periodontitis case if interdental CAL is detectable at ≥2 non-adjacent teeth, or buccal or oral CAL ≥3 mm with pocketing >3 mm is detectable at ≥2 teeth and the observed CAL cannot be ascribed to non-periodontal causes.[25]

The disease is usually asymptomatic in its early stages and many patients are unaware of the condition. Advanced periodontitis is characterized by increased mobility of teeth, tooth migration and tooth loss which leads to edentulism and masticatory dysfunction, thereby affecting the nutrition, aesthetics, speech and quality of life.[26]

Periodontitis is very common and the Global Burden of Disease Study (1990–2010) indicates that the prevalence of severe periodontitis was 11.2 %, representing the sixth-most prevalent condition in the world.[26]

Periodontitis is an escalating burden to the healthcare economy and on a global scale, periodontitis is estimated to cost $54 billion in direct treatment costs and a further $25 billion in indirect costs.[27]

Amongst the various risk factors associated with periodontitis, Diabetes mellitus has been recognized as an important risk factor for periodontal diseases and associated with significantly higher prevalence and severity of periodontitis. DM represents an enormous public health challenge and is by far the principal systemic disease affecting periodontitis in terms of extent of population affected.[28]

DIABETES MELLITUS

Diabetes mellitus consists of a group of metabolic disorders characterized by elevated blood glucose levels due to resistance to insulin action, insufficient insulin secretion, or both[29] and is associated with abnormalities in the metabolism of carbohydrates, fats and proteins.[30]The symptoms of untreated diabetes are thirst, polyuria,weight loss, sometimes with polyphagia, and blurring of vision. Acute complications of uncontrolled diabetes include ketoacidosis or the nonketotic hyperosmolar syndrome and chronic hyperglycemia is associated with long term microvascular complications like retinopathy, nephropathy, peripheral neuropathy and autonomic neuropathy, as well as an increased incidence of macrovascular complications like atherosclerotic cardiovascular, peripheral arterial, and cerebrovascular diseases.[31]

Diabetes is classified as Type 1, Type 2, Gestational diabetes and other specific types.[32]

Type 1 diabetes, which accounts for only 5–10% of those with diabetes, occurs due to autoimmune destruction of β-cells of pancreas leading to absolute insulin deficiency. This form of diabetes commonly found in children and adolescents but can also occur in adults.[29]

Type 2 diabetes is the most type of diabetes accounting for 90-95% of diabetes and is characterized by insulin resistance and/or abnormal insulin secretion, either of which may predominate. Type 2 diabetes is a multifactorial disease associated with many risk factors like age, obesity, unhealthy lifestyles and prior gestational diabetes. It commonly occurs in adults but can also be found in children and adolescents.[30,33]Gestational diabetes mellitus is defined as hyperglycemia when first recognized in pregnancy.[29] Other specific types includes a wide range of conditions with different etiologies which result in hyperglycemia e.g., monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis), and drug- or chemical-induced diabetes (such as with glucocorticoid use, in the treatment of HIV/AIDS, or after organ transplantation).[32]

In presence of obvious symptoms or acute complications the diagnosis of diabetes is confirmed by elevated glycemia levels. However in many patients, particularly Type 2 diabetes, the disease may be asymptomatic and hyperglycemia is detected during routine laboratory investigations.[30]

The diagnosis of diabetes is based on plasma glucose criteria, either the fasting plasma glucose (FPG) value [FPG≥126mg/dL (7.0mmol/L)] or the 2-h plasma glucose (2-h PG) value during a 75-g oral glucose tolerance test (OGTT)[PG≥200mg/dL (11.1 mmol/L)] or A1C criteria[A1C ≥6.5% (48 mmol/mol)],or in a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).[32]

Globally, the prevalence of diabetes is high and in 2019 an estimated 463 million adults(aged 20-79 years), representing 9.3 % of the world's population in this age group, were living with diabetes .The numbers are expected to rise to 700 million by 2045.

Diabetes inflicts a significant burden on global healthcare system and an annual spending on diabetes is estimated to be about $760 billion(2019).[34]

Prediabetes is the term used for individuals whose glucose levels do not meet the criteria for diabetes but is too high to be considered normal.Prediabetes is associated with obesity (especially abdominal or visceral obesity), dyslipidemia with high triglycerides and/or low HDL cholesterol, and hypertension and it places an individual at an increased risk for diabetes and cardiovascular disease (CVD).[32]

Prediabetes can be diagnosed by the presence of Impaired fasting glucose (IFG110–125 mg/dL) and/or impaired glucose tolerance test (IGT 2-h plasma glucose (2-h PG) in 140–199 mg/dL during 75-g OGTT) and/or HbA1c ≥5.7%–6.4%.(39–47 mmol/mol).[32,35]

EFFECT OF DIABETES ON PERIODONTAL HEALTH

Numerous epidemiological studies have shown that Diabetes mellitus(DM) is a major risk factor for periodontal disease and is associated with increased incidence, prevalence, severity and progression of periodontitis.[36-40] DM is by far the principal systemic disease affecting periodontitis in terms of extent of population affected.[41]

According to the latest classification of periodontal and peri-implant diseases and conditions uncontrolled diabetes is an important modifying factor in the clinical diagnosis of periodontitis, and is included as a descriptor in the staging and grading process as the level of glycemic control in diabetes influences the grading of periodontitis.[42]

However, in the last few years it has become evident that only poorly or uncontrolled DM predisposes to periodontal disease rather than the mere diagnosis of DM.[43-48] and the severity of periodontitis (PPD) is related to hyperglycemia in a dose-response manner (i.e., the higher the

blood glucose level is over time, the greater are the adverse effects of diabetes on periodontal health).Moreover, patients with well controlled DM have periodontal health similar to those without DM.[8,37,49]

The evidence on the effect of DM on periodontal disease was initially provided by Belting et al. in 1964[50] although studies documenting the relationship between diabetes and periodontal disease existed much before.

The main evidence of diabetes as a risk factor for periodontitis came from studies investigating Pima Indian population[51-53], an indigenous community with the world's highest incidence and prevalence of type 2 DM[54] and the studies revealed that patients with DM are approximately 3-4 times more likely to develop periodontal disease than non-diabetic subjects.[55,56] In 1993 Dr. Harold Loe labeled periodontitis as 6th complication of diabetes.[39]

A cross sectional study utilizing data from the National Health and Nutrition Examination Study III analyzed the association between glycemic control of type 2 diabetes mellitus and severe periodontal disease in 43 persons aged 45– 90 years in the US adult population. Individuals with poorly controlled diabetes had a significantly higher prevalence of severe periodontitis than those without diabetes (odds ratio=2.90; 95% CI: 1.40, 6.03). For the better controlled diabetes subjects, there was a tendency for a higher prevalence of severe periodontitis (odds ratio=1.56; 95% CI: 0.90, 2.68).[57]

Andriankaja et al performed a study to assess the association between prediabetes and gingival and/or periodontal inflammation. Findings from the study suggested that IFG and/or prediabetes are strongly associated with BOP, a marker of chronic gingival/periodontal inflammation.[58]

In a study examining 700 children and adolescents, 6–18 years of age which included 350 children with diabetes (cases) and 350 non-diabetic controls, the authors found that diabetes was associated with increased gingival bleeding and attachment loss and the association was statistically significant.[59]

In a population based prospective cohort study in Germany, which included patients with type 1 DM and type 2 DM (both controlled and uncontrolled DM) as well as diabetes free individuals, the participants were followed for a period of 5 years to determine the influence of both diabetes etiology (type 1 DM vs type 2 DM) and glycemic control on periodontal disease progression rates. The authors concluded that patients with poorly controlled type 1 DM and type 2 DM had increased rates of attachment loss progression(mean full-mouth AL increases of ~0.35 mm during 5 years of follow-up) as compared to patients with good glycemia control and healthy participants and the findings were statistically significant. The study also revealed that uncontrolled diabetes is associated with a 1.3– 3.0-fold increase in the risk for future tooth loss.[60]

In an another 5 year follow up study 92 participants were examined to determine the association between glycemic control status and progression of periodontitis and tooth loss during periodontal maintenance study. After matching for sex and smoking, the Individuals were divided into three groups: 23 individuals with diabetes and poor glycemic control (PGC), 23 individuals with diabetes and good glycemic control (GGC), and 46 controls with no diabetes (NDC). After the 5-year interval individuals with PGC had higher progression of periodontitis and tooth loss compared to NDC and GGC individuals.[61]

The adverse effect of DM on periodontal health has been confirmed by various systemic reviews and meta analysis.[62-65]

According to a 2020 systematic review and meta-analysis of 19 studies analyzing the association between periodontal disease and diabetes and hyperglycemia revealed that T1DM is a relevant risk factor for the development of PD. The proportion of patients affected by PD is more than doubled in subjects with T1DM in comparison with non-diabetic individual, and among patients with T1DM, PD seems to be more severe and the differences appear very wide between subjects in optimal and suboptimal glycemic control.[66]

A 2021 systematic review and meta-analysis of 23 articles with a total sample size of 3429 by Jensen et al., in which the effect of type 1 DM on severity of periodontal disease risk markers in children and adolescents was analyzed, revealed that in children and adolescents with T1D risk markers for periodontal disease like plaque index, gingival index, bleeding on probing, probing depth and clinical attachment loss was more pronounced as compared to their healthy controls.[67]

Wu et al. conducted a systemic review and meta-anlysis of 53 observational studies in which the relationship between type 2 DM and periodontitis was investigated. The authors concluded that type 2 DM and periodontitis are risk factors for each other and the association between the two diseases was strong.[68]

In 2013 Katagiri S, et al. examined the effect of improved glycemic control (by glycemic intervention therapy) without periodontal therapy on periodontitis in 35 type 2 diabetic patients. HbA1c, high-sensitivity C-reactive protein (hs-CRP), bleeding on probing (BOP), probing pocket depth (PPD) and community periodontal index (CPI) codes were examined at baseline, and 2 and 6 months. After the intervention therapy it was found for the first time that effective glycemic control without periodontal treatment improved bleeding on probing in type 2 diabetic patients.[69]

Evidence of the adverse effects of diabetes on periodontal health is also provided by *in vitro* and animal studies.[70,71]

Studies in humans with diabetes clearly indicate that diabetes potentiate inflammatory responses and induce apoptosis of matrix-producing cells via dysregulation of tumor necrosis factor and the formation of advanced glycation products, both of which occur at higher levels in diabetic humans .These processes result in an enhanced severity of periodontal inflammation as well as compromised wound healing thus increasing the risk of periodontal diseases.[72]

In an animal model of ligature induced periodontal disease, diabetic rats demonstrated an enhanced destruction of connective tissue apparatus and impaired healing of the affected tissue caused by an exaggerated inflammatory response in both epithelial and connective tissue.[73]

EFFECT OF PERIODONTAL DISEASES ON DIABETES

The Periodontal bacteria induce an inflammatory response within the periodontal tissues to eliminate the bacterial infection. However if the bacterial challenge persists the infection may become chronic leading to perpetuation of inflammation. Bacteria, bacterial virulence factors such as lipopolysaccharide (LPS), peptidoglycan (PGN), and other cell surface components and inflammatory mediators disseminate via the circulation and can induce significant systemic inflammation. This chronic systemic inflammatory burden is associated with an increased risk of various systemic diseases including diabetes mellitus.[74]

Evidence from various observational studies suggests that periodontal infection is associated with incident DM, negative effects on diabetic state, including poor glycemia control and increased risk of diabetic complication.[63,75,76] Moreover interventional studies among people with type 2 diabetes report an improvement in the blood glucose levels following periodontal therapy.[77,78]

In the nationally representative sample of National Health and Nutrition Examination Survey (NHANES I), Demmer et al. investigated whether baseline periodontal disease independently predicts incident diabetes.

Data from 9,296 nondiabetic male and female participants aged 25–74 years who completed a baseline dental examination and had at least one follow-up evaluation was used in the study. Subjects were classified into six categories of periodontal disease severity using the periodontal index. During a follow-up period of 17±4 years (range 1–22 years), 817 incident diabetes cases were reported and the adjusted odds ratios (ORs) for incident diabetes in periodontal index categories 3,4 and 5 were 2.26 (95% CI 1.56 –3.27), 1.71 (1.0 –2.69), and 1.50 (0.99 –2.27), respectively The authors concluded that baseline periodontal disease is an independent predictor of incident type 2 diabetes in a large, population-based sample representative of U.S. adults. Limitations of the study include lack of fasting glucose measures to exclude undiagnosed diabetes at baseline.[79]

In a population-based longitudinal study in Germany, Demmer et al. examined whether baseline clinical periodontal status is associated with A1c progression among diabetes- free individuals over a period of 5 years. Participants with poor baseline periodontal health experienced an approximate 0.08% greater increase in ΔA1C during 5 years of follow-up when compared with individuals with healthy periodontium.The authors concluded that poor periodontal health, as well as progression of periodontal disease predicts progression of A1C among diabetes- free individuals and the findings suggest that chronic infections might contribute to diabetogenesis.[80]

However in a longitudinal study demonstrating an association between perioidontitis and incident DM, the authors concluded that the findings do not indicate an apparent association between periodontitis and incident diabetes, although there was a tendency for increased risk.[81]

Saito et al. conducted a study examining the relationship between periodontitis and glucose tolerance status, including changes in status. This cross sectional study examined the data of 591 subjects for whom OGTT results in 1988 were available. In this study 415 subjects had normal glucose tolerance in 1988, and the relationship between periodontal conditions and the development of glucose intolerance between 1988 and 1998 was analyzed. In 1998, following the method of the Third National Health and Nutrition Examination Survey (NHANES III), a periodontal examination was performed. The authors concluded that deep pockets are significantly associated with the development of glucose intolerance from normal status than the past glucose tolerance status itself and the study suggests that periodontal disease is a risk factor for type 2 diabetes.[82]

In a cross sectional study utilizing data from National Health and Nutrition Examination Survey III Choi et al. demonstrated that chronic periodontitis assessed by CAL and pocket depth is positively associated with IFG and diabetes in a dose-dependent manner in a representative sample of U.S. adults.[83]

Many studies have demonstrated that periodontal disease is associated with gestational diabetes mellitus.[84-86]

Xiong et al. conducted a case control study to examine the relationship between periodontal disease and gestational diabetes mellitus (GDM). 53 pregnant women with GDM and 106 pregnant women without GDM were enrolled for the study. Full mouth periodontal examination was performed on all the participants and GDM was diagnosed by oral glucose tolerance test (OGTT). The authors concluded that periodontal disease is associated with an enhanced risk of GDM and the risk increased with increase in the severity of periodontal disease in a dose-response manner.[87]

The first evidence confirming that severe periodontitis is associated with an increased risk of poor glycemic control was demonstrated by Taylor et al.in a follow up study investigating individuals in the Gila River Indian community. Medical and dental examinations of dentate subjects aged 18 to 67 years were conducted at baseline and 2-year intervals. At a minimum follow up of 2 years, the authors found that severe periodontits was associated with increased risk of poor glycemic control indicating that severe periodontitis is a risk factor for poor metabolic control in DM.[88]

Collin et al. conducted a case control study to examine the association between periodontal disease and type 2 diabetes mellitus. The periodontal status of 25 patients with type 2 DM (age range 58 to 76) was investigated and compared with 40 non-diabetic control subjects (age range 59 to 77). Patients with type 2 had significantly more often advanced periodontitis than control subjects, 40.0% and 12.5%, respectively and advanced periodontitis was associated with worsening of HbA_{IC} level .The authors concluded that advanced periodontitis seems to be associated with the impairment of the diabetic control in patients with type 2 DM.[89]

Animal studies have also demonstrated the effects of periodontits and diabetes and it has been found that periodontits is associated with increased glucose intolerance, increased fasting glucose and insulin resistance.[90]

Many studies have reported that periodontitis is associated with an increased prevalence and severity of diabetic complications, including retinopathy, diabetic neuropathy, proteinuria and cardiovascular complications.[91]

Thorstensson et al. conducted a case contol study in which medical status of two groups of diabetic individuals, one with no/minor periodontal disease (control) and one with severe periodontal disease (case), was examined. 39 case-control pairs were selected and medical variables were analysed at baseline and at the median follow up period of 6 years. The authors found that the cases had significantly higher prevalence of proteinuria and cardiovascular complications such as stroke, TIA, angina, myocardial infarct and intermittent claudication in compatrison to the controls at follow up examination.[92]

In a longitudinal study of 628 individuals aged ≥35 years, Saremi et al examined the effect of periodontal disease on overall and cardiovascular disease mortality in Pima Indians with type 2 diabetes. During follow-up, which averaged 11 years, the results of the study revealed that the death rate from IHD was 2.3 (0.9 –5.8) times high and the death rate from diabetic nephropathy was 8.5 (1.1– 65.0) times high in subjects with severe periodontal disease as compared with those with less severe periodontal disease (no or mild and moderate periodontal disease combined), after adjustment for age, sex, and duration of diabetes. The combined death rates from cardiorenal causes (IHD and nephropathy combined) in diabetic Pima Indians with severe periodontal disease were 3.2 times higher than in those with no or mild periodontal disease or moderate periodontal disease. The authors concluded that periodontal disease is a strong predictor of death from cardiorenal disease in those with type 2 diabetes.[93]

In an another longitudinal study, consisting of 529 individuals residing in the Gila River Indian Community aged ≥ 25 years with type 2 diabetes, Shultis et al. investigated the effect of periodontitis on development of overt nephropathy, defined as macroalbuminuria, and end-stage renal disease (ESRD) in type 2 diabetes. At the end of follow-up period of up to 22 years, the incidences of macroalbuminuria were 2.0, 2.1, and 2.6 times as high in individuals with moderate or severe periodontitis or those who were edentulous, respectively, compared with those with none/mild periodontitis (P=0.01). Incidences of ESRD in individuals with moderate or severe periodontitis or in those who were edentulous were 2.3, 3.5, and 4.9 times as high, respectively, compared with those with none/mild periodontitis (P= 0.02).

The authors concluded that periodontitis predicts the development of overt nephropathy and ESRD in a dose dependent manner in individuals with little or no preexisting kidney disease.[94]

In 2013, Borgnakke et al. conducted the first systematic review of 17 epidemiologic non-interventional studies for effects of periodontal disease on diabetes control, the development of complications and the incident diabetes. The results of the study indicate that a small body of evidence supports significant, adverse effects of periodontal disease on glycaemic control, diabetes complications, and development of type 2 (and possibly gestational) diabetes. Limitations of this review are a limited number of eligible studies (only 17), several of which included small sample sizes and variations in case definition of periodontitis among studies. The authors concluded that current evidence suggests that periodontal disease adversely affects diabetes outcomes, and that further longitudinal studies are warranted.[95]

More evidence regarding the effects of periodontal infection on metabolic control of diabetes comes from treatment studies using non-surgical periodontal therapy. While some studies reported an improvement in glycemic control[96-100] others failed to demonstrate a statistically significant impact on changes in HbA1c levels following non surgical periodontal therapy.[101-104]

Grossi et al. performed a study to assess the effects of nonsurgical periodontal treatment on the level of metabolic control of diabetes. 113 Native Americans (81 females and 32 males) suffering from periodontal disease and type 2 diabetes mellitus were divided into 5 treatment groups. Periodontal assessments and blood glucose monitoring was performed before and at 3 and 6 months after treatment. At 3 months, treatment groups receiving non surgical periodontal treatment and systemic doxycycline showed significant reductions (P < or = 0.04) in mean HbA1c reaching nearly 10% from the pretreatment value The authors concluded that the effective treatment of periodontal infection and reduction of periodontal inflammation is associated with a significant improvement in glycemic control in type 2 DM.[105]

Kiran et al. investigated the effect of improved periodontal health on metabolic control in type 2 diabetes mellitus (DM) patients. Fourty four patients with type 2 DM participated in the study and were divided into two groups with one receiving non surgical periodontal treatment while as other group served as control(no periodontal treatment). The periodontal assessment and metabolic measurements were recorded in all participants at baseline (day 0) and 3rd months following the periodontal treatment in both groups. Besides improvement in periodontal parameters, the treatment group showed a significant reduction in HbA1c levels at 3 months post treatment. The authors concluded that non-surgical periodontal treatment is associated with improved diabetes metabolic control.[106]

On the contrary, a 6-month, single-masked, randomized, multi-center clinical trial performed by Engebretson et al., involving five hundred fourteen participants, did not find any improvement in glycemic control in patients with DM and moderate to advanced chronic periodontitis following nonsurgical periodontal treatment.[107]

Evidence from Systemic reviews and meta-analysis have also demonstrated that an improvement in metabolic control occurs with nonsurgical periodontal therapy.[108-113]

In 2010, Teeuw et al. conducted a systematic review and meta-analysis to explore the evidence that periodontal therapy leads to the improvement of glycemic control in diabetic patients. The meta-analysis included five studies with 371 patients. The meta-analysis demonstrated that periodontal therapy can reduce A1C levels on average by 0.40% more than in nonintervention control subjects. The authors concluded that periodontal treatment leads to an improvement of glycemic control in type 2 diabetic patients for at least 3 months. However the results should be viewed with caution due to heterogeneity among studies.[114]

A 2010 cochrane review revealed that an estimate mean percentage reduction of 0.4% in HbA1c is associated with the treatment of periodontal disease and the authors concluded that there is some evidence that treatment of periodontal disease may have a modest but favorable effect on metabolic control in people with diabetes. However the data available is extremely limited and larger, carefully conducted and reported studies are needed. [115]

In a 2015 cochrane systematic review and meta-analysis, Simpson et al. assessed 35 studies including 2565 participants to observe the effects of of periodontal therapy on glycaemic control in people with diabetes mellitus. The study revealed that there is low quality evidence that the treatment of periodontal disease by SRP does improve glycaemic control in people with diabetes, with a mean percentage reduction in HbA1c of 0.29% at 3-4 months; however, there is insufficient evidence to demonstrate that this is maintained after 4 months.[116]

In a systematic review (SR) of previous systematic reviews, Hasuike et al. analyzed 9 SRs to examine the effect of periodontal treatment on diabetes outcomes. The authors conclude that there is a significant effect of periodontal treatment on improvement of HbA1c in diabetes patients, although the effect size is extremely small. Moreover, the supporting evidence cannot be regarded as high quality.[117]

Ata-Ali et al. conducted a comprehensive review of meta-analyses to evaluate the effect of periodontal treatment on glycemic control in patients with type 2 diabetes . A meta-analysis of 11 primary studies comprising a total of 1341 participants was carried out and the results revealed a statistically significant reductions in HbA1c values [-0.32% (3.5 mmol/ mol); 95%CI: -0.50 to -0.15] and FPG values (-11.59 mg/dl; 95%CI: -15.16 to -8.01). The authors concluded that periodontal treatment is associated with improved glycemic control in patients with type 2 diabetes after a follow-up period of at least three months.[118]

MECHANISMS BY WHICH PERIODONTAL DISEASES MAY AFFECT DM

Periodontal diseases are chronic inflammatory diseases associated with dysbiotic periodontal microbiota that affect the supporting tissues of the teeth. Periodontal diseases are initiated by bacteria present in the dental plaque which react with host immune system resulting in inflammation and disease.[17]

The host immune-inflammatory response to the plaque bacteria accounts for the majority of the tissue damage and is represented by infiltration of periodontal tissues by neutrophils, macrophages and lymphocytes, and the generation of high concentrations of cytokines (IL-1β,TNF-α,IL-6,RANKL/OPG), eicosanoids(prostaglandin E2) and destructive enzymes(matrix metalloproteinases).[119]

However, the effects of periodontal diseases are not restricted to the periodontium. Inflamed periodontal tissue, the total surface area of which may amount to 15 to 20 cm^2 in severe periodontitis(which approximates the size of the palm of an adult hand) and regions of ulceration in the pocket place the bacterial biofilm in close proximity to the circulation.[120] The inflamed periodontium acts as a source of bacteria, bacterial virulence factors(like lipopolysaccharides) and inflammatory mediators which upon gaining access to the blood circulation produce distant systemic pro inflammatory effects at target tissues and organs.[121] Periodontitis contributes to the chronic, systemic inflammatory burden by eliciting bacteraemia, systemic inflammatory responses or cross-reactivity leading to auto-immune reactions.[122]At least three pathways have been proposed that may link periodontal infection to systemic disease.[123]

1. Metastatic infection caused by transient bacteremia;

2. Metastatic injury due to circulating oral microbial toxins like lipopolysaccharide (LPS) ;

3. Metastatic inflammation which arises due to formation of antigen-antibody complexes which result in a variety of acute and chronic inflammatory reactions at the sites of deposition.[124]

Invasive dental procedures and routine daily activities like mastication and tooth brushing pose a risk for bacteremia and its incidence, duration and magnitude depends upon the degree of periodontal inflammation. Data from various studies suggest that poor oral hygiene and gingivitis is associated with an increased incidence of bacteremia which indicates that gingival sulcus is the main source and portal from which different oral bacterial species gain entrance to the blood circulation.[125-128]

The mechanistic studies have investigated the role of both host inflammatory mediators and periodontal microbiota associated with periodontitis on diabetes mellitus.[129]

Role of inflammation

Chronic periodontal infection is characterized by elevation of pro inflammatory cytokines such as IL-6[130,131],TNF-α[132-134],IL-1β[132]and acute phase proteins like CRP.[131,135-137] in systemic circulation as well as in gingival crevicular fluid (GCF).[138]

Moreover, various studies have demonstrated a reduction in the serum concentration of proinflammatory mediators as well as acute phase reactants following periodontal therapy.[139-146]

Chronic, systemic subclinical inflammation such as periodontal disease has been shown to be associated with the development of insulin resistance, diabetes, and its complications. Both type 1 and type 2 diabetes mellitus are associated with elevated levels of systemic markers of inflammation.[147] Infiltration of pancreatic islets by Inflammatory cells like CD8 + T lymphocytes with accompanying inflammatory reaction involving high levels of the proinflammatory cytokines IL-1, TNF-α (tumor necrosis factor-α) and INF-γ (interferon-γ)[148,149]are responsible for autoimmune destruction of islet -β cells in type 1 DM where as impaired β- cell function and tissue insulin resistance secondary to systemic inflammation is responsible for development of type 2 DM.[150-153]

Dysregulated inflammatory host response as revealed by elevated plasma concentration of pro-inflammatory mediators, such as tumour necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6),adiponectin, CRP, and IL-10, is considered a central pathogenic factor in diabetes.[129,147,150,152,154]

Proinflammatory cytokines such as TNF-α ,IL-6 and IL-1β activate intracellular pathways like JNK and IKKβ/NF-κB through classical receptor-mediated mechanisms that promote the development of insulin resistance. JNK and IKKβ/NF-κB are also activated by pattern recognition receptors, defined as surface proteins that recognize foreign substances. These include the TLRs (activated by LPS) and the receptor for advanced glycation end products (RAGE)[activated by endogenous advanced glycation end products (AGEs)]. In addition cellular stresses like ROS and ER stress also activate JNK and NF-κB.[155]

Activation of JNK and IKKβ/NF-κB play important roles in inflammation-induced insulin resistance via different mechanisms. JNK has been shown to promote insulin resistance through the phosphorylation of serine residues in Insulin Receptor Substrate-1 (IRS-1) 1(IRS-1) where as IKKβ causes insulin resistance through transcriptional activation of NF-κB. NF-κB translocates into the nucleus, where it promotes the expression of numerous target genes whose products induce insulin resistance.[151,155]

CRP may contribute to the development of insulin resistance by activation of cytokines and complement proteins, although the mechanism is not fully understood.[156]

The possible role of inflammation in the etiology of diabetes has been supported by several prospective studies which demonstrated elevated markers of inflammation in subjects who developed diabetes during the follow-up period at the baseline examination compared with subjects who did not develop the disease .[157,158]

The role of proinflammatory mediators in diabetes mellitus has also been demonstrated in various invitro studies[159, 160], animal models of diabetes mellitus[161,162] and human studies.[163]

The mechanisms, by which periodontal infection could contribute to the development of Type 2 diabetes and its complications, are perhaps best understood by considering the emerging evidence regarding the systemic effects of obesity. Obesity is a major risk factor for diabetes, cardiovascular disease, and periodontal disease. In obese patients adipocytes secrete several proinflammatory cytokines including TNF, leptin, and interleukin-1.[164] Subjects with periodontitis also have a higher concentration of proinflammatory cytokines, such as TNF-α in serum as well as GCF as compared to periodontally healthy subjects. TNF-α suppresses insulin action via its specific receptor exacerbating insulin resistance and periodontal therapy may improve metabolic control of diabetes through improved insulin sensitivity by reducing peripheral TNF-α concentration. Therefore, a common link connecting periodontitis, type 2 DM and obesity is chronic inflammation characterized by an increased expression of proinflammatory cytokines.[165-167]

The above mentioned hypothesis is supported by experimental animal models of obesity in which the effect of periodontitis on the onset of insulin resistance and type 2 DM was determined when rats were fed a high fat or low fat diet. The results revealed that periodontitis accelerated the onset of severe insulin resistance in Zucker Diabetic Fatty (ZDF) rats fed a high fat diet suggesting that periodontits and the associated production of proinflammatory cytokines might be a facilitating factor in the enhanced development of insulin resistance and type 2 DM in obese subjects.[168,169]

In a rodent model of experimental diabetes, Hotamisligil et al administered a recombinant TNF-α receptor- immunoglobulin G chimeric protein to Zucker fatty rats to inhibit the expression of TNF-α. The authors reported an improvement in insulin sensitivity as well glucose and fatty acid levels which suggest that this cytokine has a direct role in the development of insulin resistance.[170]

Role of microbial factors

Several studies suggest that oral microorganisms may play an important role in the progression of several chronic diseases involving other parts of the body including diabetes mellitus by influencing systemic inflammation.[171-173]

The influence of periodontal microbiota on diabetes or glycaemic control was examined by Makiura et al in a study of 30 Japanese adults with chronic periodontitis and type 2 DM. Non surgical periodontal treatment was performed in all participants and subgingival microbial samples were collected at base line and for a period of 12 months. Periodontal measurements and metabolic parameters including glycated hemoglobin A1c (HbA1c) were also recorded. P. gingivalis (especially clones with type II fimbriae) was detected more frequently in subjects with increased HbA1c values after periodontal treatment than in those patients with decreased HbA1c values. The authors suggested that glycemic level in diabetes is affected by the persistence of P. gingivalis.[174]

Nishihara et al. conducted a study to compare the inflammatory response to Porphyromonas gingivalis infection in normal and diabetic mice. Porphyromonas gingivalis were inoculated adjacent to the periosteum in normal and diabetic mice. After induction, the levels of

tumor necrosis factor-α, interleukin-6 and adiponectin in the mice were measured . The diabetic mice showed significant increases in blood glucose, serum tumor necrosis factor-α and interleukin-6 levels after inoculation with Porphyromonas gingivalis, and a significant decrease in adiponectin to 35.7% suggesting a link between diabetes mellitus and Porphyromonas gingivalis infection.[175]

A study comparing cell numbers of P. gingivalis, T. denticola, T. forsythia and Aggregatibacter actinomycetemcomitans in gingival sulcus of healthy, gingivitis and periodontitis sites of non-diabetes mellitus (NDM), controlled and poorly controlled insulin-dependent DM (CDM and PDM) patients with generalized chronic periodontitis concluded that poor metabolic control in diabetic individuals is associated with increasing cell numbers of red complex bacteria in subgingival biofilm.[176]

More recent studies have also demonstrated a significant differences between the oral microbial composition of diabetic and healthy controls.[177,178]

However, other studies investigating the relationship between the oral Microbiota and Type 2DM did not find significant differences between the microbiome composition of healthy and diabetic individuals.[129,179]

Moreover, lipopolysaccharides (LPS) originating from periodontal pathogens binds to the pattern recognition receptor, Toll-like receptor 4 (TLR4), expressed by macrophages, hepatocytes and pancreatic β-cells and results in upregulation of the transcription of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin (IL)-6 and IL-1β which subsequently induce insulin resistance.[180]

Mice with periodontitis and a TLR4 loss-of-function (LOF) mutation developed less alveolar bone loss , showed an improved glucose homeostasis as well as decreased expression of tumor necrosis factor-α (TNF-α) as compared to control animals when fed on a high fat diet[181].

A recent study reported that serum IgG titers against P. gingivalis were correlated with CRP in Japanese type 2 diabetic subjects.[181]

Periodontitis associated endotoxemia can be measured directly as elevated concentrations of lipopolysaccharide (LPS) or by indirect methods determining endotoxemia, such as elevated concentrations of serum LPS binding protein, soluble CD14, and antibodies to LPS of periodontal pathogens as these serum markers are present in elevated concentrations in periodontitis patients compared with healthy subjects.[182]

Since acute infections induce severe and longlasting insulin resistance and are associated with poor metabolic control in diabetic patients[183-185],it is reasonable to suggest that chronic inflammation associated with periodontal infection which is characterized by elevated proinflammatory mediators could also lead to insulin resistance, aggravate metabolic control and other complications of DM.[164]

MECHANISMS BY WHICH DIABETES MAY HAVE ADVERSE EFFECT ON PERIODONTAL HEALTH

The biological mechanisms by which diabetes may adversely affect periodontal health include (i) microbial factors, (ii) pro-inflammatory mediators, (iii) altered immune cell function, (iv) hyperglycaemia, (v) advanced glycation end-products (AGEs) and their corresponding receptor (RAGE), and (vi) altered homeostasis of the alveolar bone.[186]

MICROBIAL FACTORS

The overall scientific evidence regarding the influence of DM on periodontal microbiota is not clear[10], although some studies have reported significant dissimilarities in subgingival microbial profiles when subjects with uncontrolled type-2 diabetes and chronic periodontitis were compared with nondiabetic subjects.[187]

PROINFLAMMATORY MEDIATORS

Various clinical and experimental studies have demonstrated that diabetic patients with periodontits have an elevated levels of proinflamatory mediators as compared with systemically healthy periodontits individuals.[129]

Poorly controlled DM is associated with an increased levels of proinflammatory mediators like interleukin [IL]-1β,PGE2, tumour necrosis factor (TNF)-α, IL-6, receptor activator of nuclear factor-kappa B ligand/osteoprotegerin in GCF as well within the gingival tissues.[188-191]

In addition to the previously mentioned pro-inflammatory mediators, adipokines such as adiponectin and visfatin are also associated with diabetes.[129]

Various invitro and animal studies have also supported the role of elevated inflammatory response in diabetes-enhanced periodontitis.

Data from invitro studies have demonstrated that DM is associated with an upregulated monocytic TNFα secretion phenotype. Monocytes from diabetic patients stimulated with Porphyromonas gingivalis lipopolysaccharide demonstrated a significantly higher TNFα production as compared to non-diabetic patients with periodontal disease. Furthermore, TNFα level was not significantly associated with the HbA_{1C} level within diabetic patients[192]

Animal model studies have shown that diabetes affects the response to P. gingivalis by prolonging inflammation, enhancing the death of fibroblasts and osteoblasts and by interfering with bone coupling in the calvarial model and in the ligature model of periodontal bone loss.[193]

Significant elevation in serum tumor necrosis factor-alpha and interleukin-6 levels and a significant decrease in adiponectin was observed in diabetic mice when Porphyromonas gingivalis was inoculated adjacent to the skull periosteum in diabetic and normal mice.[175]

In an animal model of DM, injection of Porphyromonas gingivalis, into connective tissue induced significantly higher inflammatory infiltrate in diabetic mice as compared with normoglycemic mice.[194]

In a similar experiment as mentioned above, the prolonged expression of chemokines was reversed by a specific TNF-α inhibitor indicating that a significant component of the inflammatory response induced by a P. gingivalis infection was due to TNF-α activity.[195]

ALTERED IMMUNE CELL FUNCTION

The evidence regarding a role of altered immune function in diabetic patients with periodontitis is limited.[129] However various clinical and animal model studies have provided evidence for aberrant neutrophil activity in patients with diabetes including defective neutrophil chemotaxis, phagocytosis and microbicidal mechanisms.[196-200]

Monocytes from patients with DM have a upregulated monocytic TNFα secretion phenotype and these cells respond to LPS from periodontal bacteria to produce significantly higher levels of IL-1b, TNF-α and PGE2 than cells from patients without diabetes.The data suggests that DM results in a monocytic phenotype that is associated with a more severe periodontal disease expression.[188,192]

Studies have also demonstrated elevated levels of pro-inflammatory T-helper type 1 (Th1)- or Th17-cytokines in sites of chronic periodontitis in diabetic patients with poor glycemia control than in well controlled subjects suggesting a role of T-cell subsets in periodontal disease.[201]

HYPERGLYCEMIA

Amongst the several mechanisms responsible for diabetes- enhanced-periodontits, hyperglycemia induced dysregulated host immunoinflammatory response and the subsequent hyperinflammatory state is responsible for most of the periodontal tissue damage.[10,129,202]

The main mechanism by which hyperglycemia leads to diabetic complications is by increased mitochondrial production of reactive oxygen species (ROS). Hyperglycemia-induced mitochondrial superoxide production activates the four damaging pathways which include the polyol pathway, increases intracellular AGE formation, activation of protein kinase C (PKC) and activation of hexosamine pathway flux.[203]

Of the above mentioned pathways that might play a role in the pathogenesis of periodontal diseases, AGEs, and RAGE have been studied the most and will be discussed separately.[202]

Activation of the polyol pathway increases susceptibility to intracellular oxidative stress by reducing the amount of reduced glutathione.[203]Studies have shown reduced levels of glutathione (GSH in saliva and periodontal tissue of patients with DM and periodontitis, compared to patients without DM and other studies also demonstrated increased levels of oxidized glutathione (GSSH) in saliva.[202]

Increased shunting through polyol pathway leads to enhanced aldose reductase activity which subsequently leads to the increased formation of proinflammatory molecules like AGEs, reactive oxygen species (ROS) and nitric oxide (NO). Use of aldose reductase inhibitors reduced protein kinase C (PKC) activation, less nuclear translocation of NFκB, and reduced expression of markers of inflammation as well as decreased production of ROS and improved bacterial killing by neutrophils.[63] In another study, therapy with aldose reductase inhibitor prevented alveolar bone loss in rats with DM.[202]

ROS cause cell damage directly and also by increasing the production of proinflammatory cytokines .Studies have reported improvement in diabetic complications by treatment of diabetic animals with antioxidants.[63]

Activation of PKC activates NFκB, factor that itself activates many proinflammatory genes leading to enhanced production of ROS and inflammation .[203] Protein kinase C (PKC) activity is also increased in patients with DM and periodontal disease.[202]

ROS are one of the main elements implicated in the development of diabetic complications and a major source of ROS in inflammatory lesions is neutrophil NADPH oxidase. Hyperglycemia and increased AGE associated with DM results in priming of neutrophils leading to oxidative stress.[204]

Reactive oxygen species also affect bone formation by regulating osteoblastic activity via pathways involving the interaction of reactive oxygen species, Wnt signalling and activation of FoxO transcription factors.[129]

Hyperglycemia alters the activity of gingival and periodontal ligament fibroblasts resulting in decreased collagen production and increased collagenolytic activity. Hyper-inflammatory response by oral epithelial cells and a priming effect on monocytes has also been reported.[129]

ADVANCED GLYCATION END-PRODUCTS (AGEs) AND THEIR CORRESPONDING RECEPTOR (RAGE)

An important chronic effect of hyperglycemia involves the irreversible nonenzymatic glycation of proteins, lipids and nucleic acids leading to the formation of AGEs which accumulate in the plasma and tissues of diabetic patients. AGEs play a central role in diabetic complications including periodontal disease[205-207]

AGEs exert their biological effects by receptor independent and receptor dependent pathways. Regarding receptor independent pathway AGEs modify extracellular matrix (ECM) proteins mainly collagen via excessive crosslinking of matrix molecules which makes collagen less soluble and resistant to digestion by proteolytic enzymes.[205,208]

Glycosylation of existing collagen at wound margins results in reduced solubility and impaired remodeling of the wound site. Studies have reported that in diabetic patients the reduced solubility of collagen can be reversed by insulin treatment. Elevated levels of AGEs and the cross linkages in collagen molecules have been demonstrated in palatal biopsies of diabetic patients.[209] AGEs in local tissue induce a range of cellular responses, such as osteoclast induced bone resorption, vascular complications and stimulation of secretion of inflammatory cytokines, collagenase and several growth factors. AGE accumulation has been demonstrated in the gingiva of diabetic patients affected by periodontits and in diabetic patients the serum levels of AGEs were found to be associated with severity of periodontal degeneration.[208]

In the receptor-dependent pathway, AGEs exert their pathogenic effects by reacting with the receptor for advanced glycation end products (RAGE).[208]

RAGE is a member of the Ig superfamily of receptors.[205] and is expressed by diverse cells, including endothelial and smooth muscle cells, lymphocytes, monocytes, and macrophages. RAGE is also identified in gingival tissues of patients with type 2 diabetes.[210,211]

The AGE receptor (RAGE) appears to mediate signal transduction through the generation of oxygen free radicals.[211]

Activation of RAGE by AGEs activate multiple signaling pathways such as MAPK, JNKs, or Cdc42/Rac resulting in upregulation of the transcription factor nuclear factorκB.[210,212] Nuclear factor-κB (NF-κB) is translocated to the nucleus where it increases transcription of a number of proteins, including proinflammatory cytokines like IL-1β,TNF-α, IL-6 as well as intercellular adhesion molecule-1 and vascular endothelial growth factor (VEGF).[205]

Data from a study performed by Schmidt et al.1996 revealed that heme oxygenase-1, a marker of enhanced oxidant stress, was increased in the gingival vasculature of diabetic mice and humans compared with non-diabetic controls suggesting that AGEs present in diabetic gingiva may be associated with a state of enhanced oxidant stress, a potential mechanism for accelerated tissue injury.[206]

Invitro and animal studies have demonstrated that AGE-RAGE interaction promotes destruction of periodontal tissue by inducing apoptosis of bone-lining cells, osteoblasts and human periodontal ligament (PDL) fibroblasts cells via generation of proinflammatory cytokines and upregulation of reactive oxygen species (ROS).[210]

RAGE is also a central cell-surface receptor for EN-RAGE (extracellular newly identified RAGE binding proteins), intracellular proteins within effector cells key in the inflammatory response such as polymorphonuclear leukocytes and monocytes. EN-RAGE upon their release from cells interacts with cellular RAGE resulting in sustained inflammatory cellular perturbation and chronic tissue injury and blockade of RAGE and/or EN-RAGEs suppresses inflammation and activation of key transcription factors such as NF-kB.[213]

In a murine model of experimental periodontits, blockade of RAGE diminished accelerated alveolar bone loss in diabetic mice and decreased generation of inflammatory cytokines and tissue-destructive matrix metalloproteinases (MMPs). The findings also revealed a decreased levels of AGEs in gingival tiissues which paralled the suppression of alveolar bone loss suggesting a role of RAGE and

exaggerated inflammatory responses in the pathogenesis of destructive periodontitis associated with diabetes.[213]

ALTERED HOMEOSTASIS OF THE ALVEOLAR BONE

Evidence from clinical studies and animal models strongly suggest that abnormalities in alveolar bone metabolism is an important pathway in the pathogenesis of periodontitis in DM.[129,209]

Diabetes affects osteoclast and osteoblasts in the periodontium by increasing the expression of inflammatory mediators like TNF-α and RANKL/osteoprotegerin (OPG) ratios and by enhancing the levels of AGEs and ROS.[214]

Diabetes causes a reduction in the number of bone-forming osteoblasts and fibroblasts by increasing bone cell apoptosis through AGE-RAGE interaction and increased ROS production. Elevated levels of proinflammatory mediators like TNF-α in animals models contributes to an increased apoptosis of osteoblasts and are associated with reduced bone healing.[214]

In murine model of experimental periodontits diabetes has been shown to increase the number of osteoclast in inflamed areas by two- to four-folds in diabetic rats compared to non-diabetic rats with periodontitis.[214]

A number of studies have reported an elevated expression of RANKL and TNF in diabetes-associated periodontal tissues. Animal model studies have demonstrated that RANK-RANKL/OPG ratios and the level of TNF-α, are critical mediators of the enhanced osteoclastogenesis in diabetes with periodontal disease.[214]

Studies have shown that RANKL and the RANKL to OPG ratio are higher in gingival crevicular fluid of poorly controlled diabetic patients with periodontitis compared to well-controlled or non-diabetic subjects with similar periodontal status.[129]

Moreover, RANKL/OPG ratio and TNF-α levels in periodontits sites in humans correspond to metabolic control in subjects with diabetes.[214]

CONCLUSION

The literature reviewed in this paper supports the two-way relationship between diabetes mellitus and periodontal disease. Diabetes is associated with enhanced prevalence and severity of periodontal disease and abnormal host response rather than altered periodontal microbiome is the primary underlying mechanism. Periodontitis adversely affects diabetic outcomes by enhancing insulin resistance via increase in systemic inflammatory burden. Periodontal treatment is associated with short improvement in glycemic levels in prediabetic and diabetic individuals. Further large, mulicentric, well designed, controlled trials are warranted to support the existing literature that periodontal treatment leads to improved diabetic outcome.

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Conflict of Interest

The authors have no proprietary, financial, or other personal interest of any nature or kind in any product, service, and/or company that is presented in this article.

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