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REVIEW

Diabetes mellitus and oral health

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Abstract The oral health is influenced by systemic health, and one of the most common chronic diseases encountered in dental practice is diabetes mellitus. Diabetes can worsen oral infections and vice versa. In the literature, periodontitis and diabetes in the young to middle-aged adults have been the most widely researched area. Understanding the patho-physiology, clinical manifestations and management of different types of orofacial diseases in diabetic patients are important to the diabetologist and the dentist for the optimal care of patients with these diseases. This review explores the inter-link between diabetes and oral health.

Keywords Diabetes mellitus · Oral health · Orofacial infections · Periodontal disease · Periodontitis

Introduction

Diabetes mellitus affected 382 million people worldwide by the year 2013, and the diabetes tsunami is expected to hit 592 million individuals globally by 2035 [1]. Diabetes affects every organ in the body, and the disease duration and severity may influence the degree of organ involvement. Similarly, the disease of a particular organ may have an impact on the course and prognosis of diabetes and its management. The oral health is influenced by systemic health and one of the most common chronic diseases encountered in the dental practice is diabetes mellitus.

Diabetes is a metabolic state with significant dysfunction of the immune system. Many aspects of the systemic immune response such as polymorphonuclear leukocyte function (leukocyte adherence, chemotaxis, and phagocytosis), bactericidal activity, response to antigen challenge, and T-lymphocyte function, are altered in diabetic individuals [2, 3]. Many studies have shown a definite relationship between chronic inflammation and the development of type 2 diabetes [4–7]. Periodontal disease in particular has a definite association with the development of type 2 diabetes, and diabetes can worsen the periodontal disease [8–10]. Understanding the patho-physiology, clinical manifestations and management of different types of orofacial infections related to diabetes are important for the diabetologist and the dentist for the optimal care of the patients with these diseases. This review attempts to discuss the inter-relationship between different orofacial infections and diabetes.

Etiology and pathogenesis of diabetes and its complications

Diabetes is broadly classified into 2 main types, namely type 1 diabetes mellitus (T1 DM) and type 2 diabetes mellitus (T2 DM). T1 DM results from the autoimmune destruction of insulin-producing pancreatic β-cells, whereas T2 DM is due to the increased cell resistance to endogenous insulin and/or its defective secretion. There are two mechanisms attributed to the pathogenesis of diabetes complications, namely polyol pathway and the advanced glycosylation end products (AGEs) formation. Polyol pathway attributes the conversion of glucose to sorbitol by

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aldose reductase enzyme that results in tissue damage and many of the diabetic complications. AGE formation occurs by the binding of glucose to proteins, lipids, and nucleic acids that result in alteration of their structure and functions, and their deposition in organs results in various organ-specific complications [11].

Orofacial disease and diabetes

Different oral problems and symptoms associated with diabetes include dry mouth, dental caries, periodontal disease and gingivitis, oral candidiasis or thrush, burning mouth syndrome, taste disorders, rhinocerebral zygomycosis (mucormycosis), aspergillosis, oral lichen planus, geographic tongue and grooved tongue, stimulating and traumatic wounds, delayed wound healing and increased incidence of infection after surgery, salivary dysfunction/xerostomia, taste and other neurosensory disorders, altered tooth eruption, and benign parotid hypertrophy [12, 13]. In the literature, relationship between periodontitis and diabetes in young to middle-aged adults (25–55 years of age) has been the most widely researched area, whereas other oral complications in diabetes and other age groups like the younger or older diabetic subjects have not been adequately represented in most studies [12].

Diabetes in the elderly patients caused higher prevalence of root caries and more profound effect of the xerogenic medications, whereas there was neither a change in the prevalence of coronal caries nor salivary flow rate among the younger subjects and controls [14]. There was higher prevalence of burning mouth syndrome, xerostomia, angular cheilitis, and glossitis among older diabetic patients who were edentulous than in the control group [15]. Diabetes is known to cause progression of periodontal disease which in turn exposes root surfaces and thus increases the risk of developing root caries [16].

Although benign parotid hypertrophy is observed in older patients with diabetes, its prevalence is unknown. The disease is due to enlargement of acinar cells as a result of an interruption in protein synthesis and release [12].

In diabetic individuals, there is limited collateral blood flow in the pulp tissues, and this results in faster aging changes of pulp than that in individuals without diabetes. Ischemia and damage to the blood circulation in diabetes also may cause pulp necrosis [17]. Inflammatory mediators produced in diabetes can result in changes in the oral tissue and structure of pulp [18]. Changes in the antioxidant system and reduced activity of the pulp tissue were seen in patients with poorly controlled diabetes mellitus [19].

In a cross-sectional study to assess if periodontitis was a significant modifier in the risk that diabetes poses for increased carotid artery intima-media wall thickness and advanced atheromatous lesions, it was found that periodontal disease can increase the risk of subclinical atherosclerotic heart disease and coronary heart disease [20].

Periodontal disease

Periodontal disease involves one or more of the periodontal tissues (alveolar bone, periodontal ligament, cementum, or gingiva). The strong dual association between diabetes and periodontal diseases such as gingivitis (inflammation of the gingiva) and periodontitis (inflammation with destruction of periodontal tissues) is well known for more than a decade. Epidemiological studies reveal that the risk of developing periodontitis is 3 times higher in diabetic patients [21]. Periodontitis is known to be a complication of both T1 DM and T2 DM. Periodontitis is also responsible for several adverse health outcomes, possibly due to the associated systemic inflammation [12]. A longitudinal study on diabetes and periodontal disease in Pima Indians ($\geq$35 years old) revealed 3.7 deaths per 1,000 persons [95 % confidence interval (CI) 0.7–6.6] among diabetics with mild or without periodontal disease, 19.6 (10.7–28.5) in moderate periodontal disease, and 28.4 (22.3–34.6) in severe periodontal disease [22].

There are well-documented papers on the inter-relationship between diabetes and periodontal health which show that diabetes can lead to poor periodontal health, and periodontal disease can hamper control of diabetes [8]. Periodontal attachment loss in patients with poorly controlled diabetes is also greater in comparison to that with well-controlled diabetes or healthy individuals [23, 24]. Although some studies have shown that management of periodontal disease may improve glycemic control, there is still a need for further evidence [25–30].

Periodontal disease can also increase the risk of developing renal and cardiovascular disease [31] and cardiorenal mortality [22] in diabetic patients as suggested by a few longitudinal observational studies.

Pathogenic inter-relationship between diabetes and periodontal disease

The two major mechanisms by which diabetes adversely affects periodontal health are by decreasing the renewal of periodontal tissues and defective local immune defence mechanism [32]. There is an increase in the production of pro-inflammatory cytokines which promotes destruction of periodontal tissues and decreased elimination of periodontal pathogens due to altered immune cell function in diabetic patients [33]. Diabetic patients are known to have increased level of AGEs in the periodontium in comparison

to non-diabetic patients [34]. The AGEs and collagen interact to produce collagen macromolecules which are highly stable and resistant to degradation by physiologic enzymes [35], and thereby reducing the renewal of periodontal tissues in diabetic patients with poor glycemic control that partly explains the reason for diabetic patients to have three times greater chance to develop periodontitis than non-diabetic patients. On the other hand, periodontitis can also have a negative impact on diabetes by contributing to insulin resistance and thus worsening glycemic control [32]. It is known that chewing can result in systemic dissemination of periodontal pathogens and their metabolic products in patients with periodontitis [36] causing endotoxemia or bacteremia which results in an increase in the serum levels of inflammatory mediators such as IL-6, fibrinogen, and C-reactive protein (CRP). Systemic inflammation is well known for worsening insulin resistance and diabetes control. In these cases, initiating periodontal therapy can result in decreased level of circulating pro-inflammatory mediators, thereby contributing to better control of glycemic status [37–40]. The patho-physiological relationship between diabetes and dental disease is shown in Fig. 1.

Microbial flora in diabetic patients with generalized chronic periodontitis

Pathogens most commonly found in periodontitis are *Porphyromonas gingivalis*, *Treponema denticola*, and *Tannerella forsythia* which together comprise the red complex. In a study by Aemaimanan et al. on quantification of *P. gingivalis*, *T. denticola*, *T. forsythia*, and *Aggregatibacter actinomycetemcomitans* in gingival sulcus of healthy non-diabetics at the sites of gingivitis and periodontitis, and in controlled and poorly controlled T1 DM patients with generalized chronic periodontitis, it was found that these pathogens were found in greater numbers in patients with poor glycemic control [41].

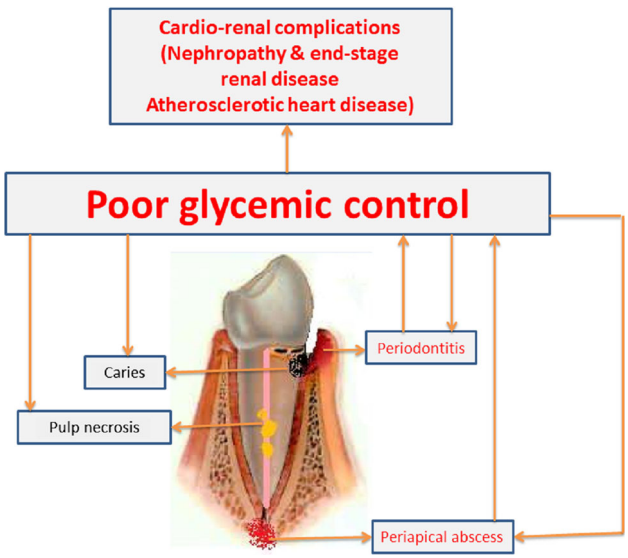

Fig. 1 Patho-physiological relationship between diabetes and dental diseases

In a cross-sectional study on 42 patients with T2 DM and periodontitis to determine the prevalence of Candida species, it was seen that the frequency of *C. albicans* was greater than that of *C. dubliniensis*, *C. tropicalis*, and *C. glabrata*. Patients with high blood sugar levels and probing pocket depth of ≥5 mm had greater Candida infections [42].

Periodontal infection, diabetes, and complications

There is emerging evidence that periodontitis is a risk factor in the development of diabetes and complications like cardio-renal mortality, nephropathy, and end-stage renal disease. A study by Saremi et al. on the risk for cardio-renal mortality in periodontal disease in 628 Pima Indians during a 11-year period revealed that in severe disease, there was 3.2 times higher risk for cardio-renal mortality than those without disease, mild disease, or moderate disease [22]. Another study by Shultis and co-workers in 529 Gila River Indian Community adults with T2 DM revealed that the risk for overt nephropathy was 2.0, 2.1, and 2.6 times higher in moderate or severe periodontal disease and edentulous individuals, respectively, in comparison to those without disease or mild periodontitis. They also found that the incidence of end-stage renal disease (ESRD) in this cohort was 2.3, 3.5, and 4.9 times higher in moderate, severe periodontitis, and those who were edentulous, respectively, compared to individuals without the disease or mild periodontitis [43].

A study on diabetic children and adolescents revealed increased destruction of periodontal tissues with a relative risk of 2.72 ($p = 0.006$) in comparison to controls without diabetes. A higher risk (3.74, $p = 0.021$) was observed in the age group 6–11 years than in the age group 12–18 years (2.63, $p = 0.066$) [44]. In this study group, the relationship between HbA1c and periodontitis was found to be significant, but no such relationship was found with respect to BMI and disease duration. Early eruption of teeth especially in the extra-alveolar phase of tooth eruption was noted in young diabetic patients than in the control group who were non-diabetic.

Periodontal disease is also known to be a risk factor for development of T2DM. A large cohort study of 7,000 individuals, which looked into the relationship between periodontal disease and incidence of T2 DM, showed that

periodontal disease significantly increased the risk by 50–100 % for T2 DM during a 17-year follow-up [10].

Gestational diabetes mellitus and periodontal disease

There is very little data available on the effects of gestational diabetes mellitus (GDM) on periodontal health, although it has been observed that the infection and inflammation associated with periodontal disease may have an adverse effect on the gestational period and on fetal growth [45–47]. In a study on 256 pregnant and 4,234 non-pregnant women with history of GDM in current pregnancy or previous pregnancy, or with T1 DM or T2 DM during pregnancy, a definite relationship between periodontal disease and diabetes was observed. Periodontitis was prevalent in 44.8 % of pregnant women with GDM and only in 13.2 % of pregnant women without diabetes (adjusted odds ratio of 9.11; 95 % CI 1.11–74.9), whereas in non-pregnant women, it was 40.3 % in T1 DM or T2 DM, 25.0 % in women who had gestational diabetes in the past and 13.9 % in women without diabetes (adjusted odds ratio 2.76; 95 % CI 1.11–7.35 for T1 and T2 DM) [48]. In another prospective study of periodontitis in postpartum women with or without a recent history of gestational diabetes, it was observed that the former group had decreased insulin sensitivity and β-cell function. Also periodontitis could cause development of impaired glucose metabolism and diabetes in future [49].

Diabetes and dental implant

Older patients with T2 DM and its co-morbidities have higher risk of developing periodontal disease with subsequent tooth loss, thereby reducing masticatory efficiency that results in poor quality of life [50]. Adequate glycemic control which is important to reduce diabetes-related co-morbidities depends on the masticatory function and tooth replacement, and implant therapy may improve the patient's quality of life. There are limited studies on implant failures in diabetic patients with poor glycemic control, although it is stated to be a relative contraindication for implant therapy [12].

Diabetes mellitus, periapical lesions, and endodontic treatment

There have been only few studies showing a link between periapical disease and diabetes. Diabetic patients have a higher prevalence of periapical lesions, greater size of the osteolytic lesions, increased likelihood of asymptomatic infections, and worse prognosis for root filled teeth. A study by Bender et al. demonstrated that periapical radiolucencies developing during treatment in diabetic patients who have poor control of their disease healed as good as in non-diabetics when the disease was well controlled [43]. The results of some studies suggest that periapical disease may contribute to poor metabolic control of diabetes.

A radiographic assessment of periapical lesions after root canal treatment in 12 patients with lowered glucose level and 13 patients with high glucose level revealed a reduction of 74 and 48 %, respectively, after 30 weeks [51]. A similar study by Falk et al. reported higher number of periapical lesions in root canal treated teeth in women with long-standing diabetes in comparison to women with short duration of diabetes and non-diabetics [52]. Multivariate analysis of endodontic diagnostic and treatment outcome in diabetic and non-diabetic patients revealed greater incidence of periodontitis in endodontically treated teeth and a decreased success rate of treatment when preoperative periradicular lesions were present [53]. The important patho-physiological aspects, treatment, and prevention of diabetes-related orofacial disease are summarized in Table 1.

Dental management in diabetic patients

Oral health promotion, evidence-based treatment strategies, routine oral screening in diabetic patients, diabetic screening in high risk groups in the dental surgery, increased awareness, and greater collaboration between healthcare professionals are of paramount importance to deliver effective management of diabetes and its related consequences on oral health [54]. According to the guidelines by The International Diabetes Federation for primary care of diabetes, patients should be enquired annually if they suffer from any symptoms of gingival disease (e.g., bleeding when brushing, swollen, or red gingiva), advised oral hygiene measures, patient education about the need to maintain good oral health to prevent gum diseases, and regular dental visits for appropriate management by the dental team are important [55]. The dental chair-side testing of gingival crevicular blood (GCB) glucose levels is a good tool to evaluate risk for T2 DM as the results are comparable to the systemic blood glucose concentration level [16].

Proper management of periodontal disease is important for appropriate control of diabetes, and vice versa. Periodontal disease was also found to have a strong association with diabetic complications such as nephropathy, stroke, ischemic heart disease, and cardiac failure [56]. Periodontal treatment has been shown to decrease periodontal inflammation which in turn may improve insulin

Table 1 Patho-physiological aspects, treatment, and prevention of diabetes-related orofacial disease

Diabetes-related oral disease	Patho-physiology	Treatment and prevention
Periodontal disease	Accumulation of advanced glycation end products (AGEs) in periodontal tissues, decreased renewal of periodontium and defective local immune regulation	Assessment of risk of disease progression, periodic dental check up, dietary advice and nutritional intervention, periodontal therapy
Dry mouth	Reduced salivary flow rate as a result of polyuria and dehydration	Proper control of diabetes and appropriate dental hygiene
Root caries	Progression of periodontal disease exposing root surface and reduced salivary flow rate predispose to enamel hypomineralization and caries formation	Fluoride application, use of fluoride containing toothpaste, restorative procedure. Optimal glycemic control helps prevention of progression
Oral candidiasis	Infection with Candida species resulting from salivary dysfunction, hyperglycemia and abnormal immune function	Anti-mycotic drugs such as nystatin and miconazole. Prompt glycemic control is preventive
Pulp necrosis and periapical abscess	Ischemic damage to pulp tissues diabetes-related vascular damage	Endodontic treatment and control of diabetes
Delayed wound healing and increased incidence of infection after surgery	Diabetes-related vascular dysfunction and decreased immune function	Antibiotics and good glycemic control

sensitivity, and thus glycemic control [33, 57]. Other studies on individuals with diabetes and periodontitis treated with non-surgical periodontal therapy and adjunctive local delivery of minocycline revealed decreased serum levels of TNF-α [58, 59]. Also, decrease in serum levels of TNF-α was observed to be strongly associated with a decrease from 8 to 7.1 % in mean glycated hemoglobin (HbA1c) values [58]. However, serum levels of TNF-α showed no significant change following 4 weeks of mechanical periodontal therapy in a pilot study by Lalla et al. This study did find a significant decrease in the systemic levels of mediators such as CRP and soluble E-selectin following treatment [60].

A study was conducted among 160 patients with T2 DM and periodontal disease (high-sensitivity c-reactive protein level: >500 ng/ml) for resolution of periodontal inflammation by conventional mechanical debridement combined with antibiotics. The results showed improved glycemic control [61]. A meta-analysis of randomized clinical trials done by Fabrizio et al. on improvement of glycaemic and metabolic control in type 2 DM with chronic periodontitis following periodontal treatment showed that scaling and root planning were effective in a reduction of HbA1c [mean difference (MD) = 0.65; 95 % CI 0.43–0.88; $p < 0.05$] and fasting plasma glucose (MD = 9.04; 95 % CI 2.17–15.9; $p < 0.05$) [62]. Another randomized study to assess the efficacy of short-term adjunctive sub-antimicrobial dose doxycycline treatment in combination with scaling and root planning in T2 DM and chronic periodontitis patients revealed improvement at tooth sites with moderate disease (PD ≥4 mm) when compared to scaling and root planning alone [63].

Costa et al. investigated the effect of glycemic control in the progression of periodontal disease and tooth loss during periodontal maintenance therapy over a period of 5 years. This study found that in subjects with poor glycemic control who were smokers, the disease progression and tooth loss were greater than in those without diabetes and diabetic subjects with good glycemic control [64].

The results of a meta-analysis of 10 intervention trials with 456 patients with diabetes (type 1 or type 2) in whom mechanical periodontal therapy was done, there was no statistically significant difference, although an average decrease of HbA1c levels of 0.38, 0.66 and 0.71 % in all studies, subjects with T2 DM and antibiotic-administered cases, respectively, were observed [26]. Anti-diabetic medications such as α-glucosidase inhibitors reduce HbA1c level by 0.5–1 %, whereas insulin secretagogues, biguanides and thiazolidinediones, diet control, and physical activity are known to reduce HbA_{1c} level by 1–2 % [65]. In this context, the decrease in HbA_{1c} level of 0.71 % from periodontal treatment and adjunctive antibiotic therapy as seen in the meta-analysis is still relevant [66].

In a randomized controlled clinical trial by Moeintaghavi et al. among 42 patients with T2 DM and chronic periodontitis, it was found that non-surgical periodontal treatment involving scaling and root planning helped improvement of metabolic control in diabetic patients [67].

There is emerging evidence in a meta-analyses of intervention studies in T2 DM patients that glycemic control improved with non-surgical periodontal therapy resulting in 0.4 % reduction of HbA1c [25, 68]. This is clinically significant as 14–21 % reduction in the diabetes-related end-points is seen with every 1 % reduction in mean HbA1c level [69]. There is also good evidence, according to Lamster, that periodontal therapy alone may

result in improved reduction in HbA1c level for a short duration of approximately 3 months [12].

Current studies advocate the use of implants even in diabetic patients who have inadequate glycemic control [70–73]; however, it needs more evaluation of potential risk and benefit in the wake of limitations in the current knowledge about the relationship between diabetes and implants [12]. Implant success rate can be improved to 85–95 % by proper case selection among diabetic patients, the absence of co-morbidities (smoking, periodontal disease, and poor oral hygiene), adequate glycaemic control (HbA1c at 7 %), and prevention of infection [74].

Variation in the medical treatment regimens used in several studies, small sample sizes, inclusion of patients with both T1 and T2 DM, confounding factors such as smoking and variations in the BMI, and study designs determining only short-term outcomes makes it difficult to interpret conflicting results from different studies on the definite link between oral disease and diabetes [67]. However, the available evidence favors a strong association that needs to be considered by diabetologists and dental practitioners.

Use of antibiotics in dental infections is not routinely recommended in clinical practice unless systemic signs of sepsis are evident. Diabetic patients have higher risk of spread of oral inflammation and systemic dissemination of infection because of the poor immune function. Although it is not indicated in all diabetes-related dental infections, antibiotics may be necessary in severe cases, especially in emergency situations where glycaemic control is poor. Prevention of systemic and local disease spread may be an advantage of such intervention in some cases [75].

The medications used for diabetes control in patients with orofacial infections and dental diseases are similar to those used in routine clinical practice for glycaemic control. However, metformin may be used with caution in severe infections because of the possibility of developing lactic acidosis in septic conditions. In severe infections, it is always ideal to use insulin for glycaemic control as the efficacy, safety, and tolerability of other anti-diabetic medications may not be predictable [76]. Sulphonylureas such as glibenclamide, gliclazide, glipizide, and glimepiride can be used in orofacial disease as in other medical conditions with diabetes although hypoglycaemia can be a serious complication in some individuals especially with co-morbidities like renal and hepatic impairments. Glucagon-like peptide-1 agonists (exenatide, liraglutide, lixisenatide, and albiglutide) and dipetidyl peptidase-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, linagliptin, and alogliptin) can also be used in glycaemic control in patients with dental diseases unless contraindicated because of other reasons.

Conclusions

Diabetes is also a pro-inflammatory state that leads on to local and systemic inflammation. On the other hand, infections and inflammatory states increase the insulin resistance and cause worsening of the diabetes control. Several studies have shown the inter-link between oral health diabetes, thereby highlighting the importance of proper management of orofacial infections in the reduction of the disease-related morbidity from diabetes and vice versa.

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