Current Oral Health Reports (2022) 9:119–125
https://doi.org/10.1007/s40496-022-00322-z

SYSTEMIC DISEASES (N BUDUNELI, SECTION EDITOR)

Type 1 Diabetes Mellitus and Periodontal Health

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Accepted: 12 October 2022 / Published online: 22 October 2022

Abstract

Purpose of Review This review examines the current literature on the possible two-way interaction between type 1 diabetes mellitus and periodontal health.

Recent Findings The literature on type 1 diabetes and periodontal disease is rather scarce and mainly involves clinical investigations in children and adolescents. However, recent studies on adult populations with type 1 diabetes suggest that both chronic inflammatory diseases affect each other negatively.

Summary Type 1 diabetes is likely to increase the risk of onset and progression of periodontal disease. Further large-scale and controlled studies on adult population are warranted to better clarify the nature as well as possible mechanisms for the relationship between type 1 diabetes mellitus and periodontal disease.

Keywords Glycated haemoglobin · Type 1 diabetes mellitus · Periodontal health · Periodontal disease

Introduction

Diabetes mellitus (DM) is one of the most common systemic diseases worldwide. It affects protein, fat, and carbohydrate metabolisms and has very important consequences on general health. The most common form of DM is type 2 DM (T2DM) that is characterised by insulin resistance leading to hyperglycaemia although there is sufficient production of insulin. Type 1 DM (T1DM), on the other hand, is an autoimmune disease that is characterised by lack of sufficient insulin production due to destruction of the pancreatic β-cells of Langerhans islets [1]. This is much less prevalent than T2DM and has an autoimmune background. T1DM was previously referred to as "juvenile diabetes" and "insulin-dependent diabetes". Genetic and non-genetic environmental factors are estimated to have a proportional role in the pathogenesis of the disease [2]. A genetic predisposition of human leukocyte antigen (HLA) with class 2 genes and a deficiency of vitamin D has been suggested to play a role in the pathogenesis of T1DM [3]. Other suspected major environmental risk factors include enterovirus infections [4, 5], nutritional factors such as early exposure to cow's milk proteins, high intake of cow's milk products in childhood, duration of breastfeeding, intake of nitrates and nitrites [6], older age of the mother, and lower birth order [7]. There is a dramatic increase in the incidence of T1DM probably due to changes in the exposure to environmental factors [8]. On the other hand, the pathogenesis of diabetes still needs unravelling and accordingly, there are no proven preventive measures [9].

Periodontal diseases are chronic inflammatory diseases that affect the tooth supporting tissues and are considered among the most common chronic infectious, inflammatory diseases globally. Periodontitis is characterised by destruction of cementum, periodontal ligament, and alveolar bone that can lead to tooth loss if left untreated. Diabetes and periodontitis are chronic inflammatory diseases that share common pathogenic mechanisms such as sustained inflammation and host-response-mediated tissue destruction. Diabetes mellitus is accepted as a risk factor for periodontitis, with higher prevalence, incidence, severity, and progression of periodontitis [10••]. Numerous studies have indicated a bidirectional relationship between T2DM and periodontal diseases, and periodontitis has been suggested as the sixth complication of T2DM [11]. Alterations in host's vascular, cellular, and repair processes in diabetic patients at least partly explain an increased risk of onset as well as

This article is part of the Topical Collection on *Systemic Diseases*

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progression of periodontal disease [12••]. It is well-known that the duration and severity of hyperglycaemia play a major role in development of diabetes complications [13]. Suggested mechanisms by which hyperglycaemia could affect periodontal disease include hyperinflammatory response to infection, uncoupling of bone destruction and repair due to more rapid collagen turnover, and the effects of advanced glycation end products [14]. Microvascular complications of diabetes are usually blamed for the harmful effects on periodontal tissues and microvascular complications may be explained by generation of advanced glycation end products (AGEs), oxidative stress, tissue specific metabolic flux dysregulations, mitochondrial dysfunction, and chronic inflammation [15]. Diffuse microangiopathy of endoneurial capillaries with resultant ischemia and alteration of the blood nerve barrier [16]. Such changes in periodontium vessels have been observed in periodontal tissues that are linked to increased bleeding tendency [17]. A recent study with the largest scale that examines oral health outcomes among adults with T1DM reported that the presence of diabetic peripheral neuropathies and poor cholesterol control were associated with increased risk of tooth loss [12••]. A US-based study reported that screening for diabetes in the dental setting was effective in identifying both prediabetes and diabetes [18]. On the other hand, a recent consensus report concluded that there is insufficient evidence on the possible association between periodontal disease and poor glycaemic control among people with T1DM [19••].

Periodontitis, on the other hand, adversely affects glycaemic control and worsens complications of DM [20••]. However, the majority of the available literature on the possible interactions between DM and periodontal disease is based on T2DM as it is more prevalent, and the age of onset is older, increasing the risk of intersection with periodontitis. However, there is an increase in the global frequency of T1DM and clarification of the possible two-way relationship is warranted. The aim of the present narrative review is to focus on T1DM and provide an up-to-date literature review on its relationship with periodontal disease.

How Does T1DM Affect Periodontal Health?

Patients with diabetes exhibit greater susceptibility for periodontal disease [21]. Bacterial challenge in an environment of enhanced expression of receptor for advanced glycation end products (RAGE) such as the periodontium of an individual with DM has been suggested to lead an exaggerated inflammation and impaired repair eventually leading to an accelerated and severe periodontal destruction [22]. Studies on T1DM mostly involve children or adolescents and there is a clear heterogeneity between the studies in terms of methods used to evaluate clinical periodontal status. Higher gingival inflammation scores have been reported in children with T1DM compared to non-diabetic controls from different geographic areas [23–25]. Moreover, higher incidence of dental plaque and earlier and heavier formation of calculus have been reported in diabetic children [26].

A systematic review of 37 original studies reported higher plaque scores and poorer periodontal health in individuals with T1DM compared to the systemically healthy controls [27]. Moreover, periodontal health in T1DM individuals deteriorated with poor metabolic control. Similarly, another recent systematic review and meta-analysis involving 23 studies [28] reported higher plaque and bleeding scores in children with T1DM in mostly cross-sectional studies that do not report the duration of DM. Dicembrini et al. [29••] also performed a systematic review on this topic with 11 studies and reported higher prevalence of periodontitis, and deeper clinical attachment levels suggesting that T1DM could be a risk factor for periodontitis. Particularly the uncontrolled T1DM patients were found to be at higher risk for developing severe periodontitis. A recent meta-analysis analysed the existing evidence regarding the relationship between periodontal status and T1DM in childhood and in adolescence [30]. Periodontal status of diabetic and non-diabetic groups was compared using gingival index, clinical attachment level, probing depth, plaque index, and bleeding on probing. Findings from the 10 eligible studies suggest that there is a positive association between T1DM and periodontal disease severity in children and adolescents with T1DM compared to that in healthy controls. However, the meta-analysis did not provide strong evidence that periodontitis is a significant risk factor for T1DM, and the link between periodontal disease and T1DM appears to be not solid as the connection with T2DM, keeping in mind that it has been investigated to a lesser extent. Overall, none of the authors of these systematic reviews was able to illustrate a cause-effect relationship between T1DM and periodontitis.

There are few longitudinal studies available, and the findings are controversial. Vascular changes are regarded as a major component of the pathogenesis of diabetes complications, which may also involve periodontal vasculature [31]. Diabetic microangiopathy may result in increased thickness but also weakness of vessel walls creating a tendency of gingival bleeding, whereas impaired immune response and a lower resistance to infections, differences in oral microflora, and disorders in collagen metabolism are suspected mechanisms underlying increased prevalence of periodontitis in diabetic patients [32]. Vascular changes in periodontal tissues decrease polymorphonuclear cell functions such as chemotaxis, adherence, phagocytosis, migration, and antigen elimination leading to progression of periodontitis [8].

Diabetic hyperglycaemia increases salivary concentration of glucose and its concentration in gingival crevicular fluid possibly increasing proliferation of periodontopathic

bacteria and concomitant oral inflammation [33–35]. Hyperglycaemia increases formation of advanced glycation end products (AGEs) that can create complex molecules, which reduce collagen solubility and increase levels of proinflammatory mediators responsible for degradation of connective tissues eventually accelerating degradation of mineralised and non-mineralised periodontal tissues [34, 36]. Furthermore, the hyperinflammatory response seen in diabetics may possibly impair wound healing contributing to further progression of periodontal tissue destruction [34].

Seventy-seven children (mean age 13.3 years) with a mean diabetes duration of 5.6 years and median HbA1c level of 8.5 were investigated for clinical periodontal status and diversity and composition of their oral microbiota [28]. The authors concluded that children with T1DM showed a continuous relationship between less favourable glycaemic control and increased early markers of periodontal disease. Moreover, glycaemic control was associated with complexity and richness of the dental plaque microbiota, and diversity was increased with increasing HbA1c levels. An increase in HbA1c was associated with a moderate increase in plaque index, gingival index, bleeding on probing, and probing depth > 3 mm. Accordingly, Merchant et al. [37] used DNA-DNA hybridisation technique and found a correlation of HbA1c with microorganisms associated with periodontal disease in children with T1DM but not with good glycaemic control.

A recent cohort study assessed the extent and severity of periodontal disease among T1DM patients and investigated its possible association with diabetic systemic markers [38••]. Patients ≥ 18 years of age, diagnosed with T1DM, and currently treated with multiple daily insulin injections (MDI) or continuous subcutaneous insulin infusion (CSII) were included in the study. All included patients were using flash glucose monitoring (FGM) device for the last 3 months prior to the study. Periodontal examination included full-mouth recordings of plaque index, bleeding on probing, probing depth, gingival recession, furcation involvements, and tooth mobility. Information regarding hygiene habits, frequency of dental appointments, smoking habits, and previous dental treatments were also collected during the patient interview. A total of 83 patients (65%) out of 133 with a mean age of 45.5 years and mean value of HbA1c 7.5 exhibited periodontitis and 3% were edentulous. Among all investigated parameters, mean clinical attachment level was associated with HbA1c ≥ 7. The ratio of T1DM patients with periodontitis was higher than that reported in a recent systematic review [29••] and the authors stated that this discrepancy could be due to the great heterogeneity in periodontal diagnosis and clinical periodontal evaluation method. The authors concluded that their findings in this well-controlled T1DM cohort may suggest a two-way relationship similarly to the one between T2DM and periodontal disease. Moreover, the authors reported a significant association between probing depth and glucose coefficient of variation (glucose CV) that could be regarded as a novel parameter for daily fluctuations in blood glucose level.

Human beta-defensin (hBD) 1–3 are antimicrobial peptides produced in gingival epithelium and released in saliva and gingival crevicular fluid [39, 40] that play a role in adaptive immune system, angiogenesis, and wound healing [41]. A recent study investigated salivary hBD-2 and hBD-3 concentrations in relation to periodontal and T1DM status in children and adolescent populations [42]. Children in four groups: periodontally healthy T1DM ($n = 18$), gingivitis and T1DM ($n = 20$), systemically and periodontally healthy ($n = 15$), and systemically healthy gingivitis ($n = 13$) were recruited for the study and basic clinical periodontal measurements were recorded in all teeth present. The findings revealed similar salivary hBD-2 and hBD-3 concentrations among periodontally healthy and gingivitis groups. However, T1DM patients had lower salivary hBD-3 concentrations regardless of gingival health status, possibly providing an explanation for the increased risk of periodontal disease development in T1DM patients.

In a case-series study, periodontal conditions, retinopathy, and serum glutamic acid decarboxylase antibody (GADA) titres were evaluated in relation to retinopathy in adult patients with T1DM [43]. Eighty-five adult patients with T1DM, who were monitored for at least 5 years, were examined and retinopathy that is one of the major complications of DM was found to be related with the duration of DM, age of the individual, and increasing severity of periodontitis. Another study comparing gingival tissue levels of AGE between groups of T1, T2 DM patients with periodontitis, systemically and periodontally healthy individuals, and systemically healthy patients with periodontitis reported significantly higher gingival AGE levels in diabetic patients that were correlated with duration of DM [44]. Increased AGE levels are likely to enhance oxidative stress, and this is a potential mechanism of increased tissue injury in diabetic patients.

Sereti et al. [45] compared gingival crevicular fluid (GCF) levels of interleukin-8 (IL-8), matrix metalloproteinase-8 (MMP-8), and AGE and reported similar values in T1DM patients and healthy controls. Possible explanation for the lack of significant difference may be the mild periodontal disease, mostly as gingivitis and the presence of little if any diabetic complications in the T1DM cohort. A recent pilot study evaluating salivary biomarkers and measures of diabetic autonomic dysfunction involved systemically healthy, T1DM, and T1DM patients with neuropathy [12••]. The authors suggested that selected salivary biomarkers, such as IgA, combined with a periodontal examination can offer a non-invasive method to assess risk for developing diabetic neuropathy in T1DM patients.

Possible effects of DM on the tooth survival after periodontal treatment were evaluated in a recent study with 4-year follow-up involving both T1 and T2 DM patients and both types of DM were found to be related with higher risk of tooth loss following periodontal treatment [46].

How Does Periodontal Treatment Affect Glycaemic Control in T1DM?

Available evidence suggests that presence of periodontitis ought to be viewed as a key risk factor for pathogenesis of diabetes [22]. Increased release of proinflammatory cytokines in circulation due to periodontal inflammation is among the major suspected mechanisms that trigger insulin resistance [47, 48]. Chronic character of periodontitis elicits cytokine sensitivity and contributes to the vulnerability to long-term complications. Periodontitis has been reported to contribute a low-grade systemic inflammation [49]. Lipopolysaccharides from periodontopathic Gram-negative bacteria are able to induce tumour necrosis factor-alpha (TNF-a) production by monocytes and macrophages and this cytokine can interfere with lipid metabolism, reduce glucose uptake by cells, and cause insulin resistance [50]. It is well known that an inflamed periodontium is highly vascular and may serve as a gate to the systemic circulation for bacterial products as well as locally produced inflammatory mediators that is among the major proposed mechanisms of adverse effects of periodontal inflammation on systemic health. Moreover, locally produced cytokines such as interleukin (IL)-2, IL-10, interferon gamma (IFN-g), and transforming growth factor (TGF) can affect release of insulin hormone and glycaemic control [51, 52]. Thus, a vicious cycle may exist between periodontal inflammation and metabolic control of diabetes. However, current data on the effects of periodontal disease on T1DM are inconclusive [19••].

There are a limited number of clinical studies evaluating the possible effects of periodontal treatment on the glycaemic control of T1DM and there is a great variability in the treatment modalities and follow-up duration is rather short. Aldridge et al. [53] performed two studies with 2-month follow-up in T1DM individuals with age ranges of 16–40 years and 20–60 years. In the first study, only gingival bleeding correlated with the change in the metabolic control, whereas the second age range group revealed no significant difference between the treated and non-treated groups in terms of metabolic control. The authors concluded that reducing periodontal inflammation resulted in no significant effect on metabolic control in T1DM patients with good metabolic control. Westfelt et al. [54] performed non-surgical and surgical periodontal treatment as required in patients with T1DM and T2DM and followed the individuals for 5 years with recalls every 3 months. Both DM groups revealed similar improvements in periodontal parameters and no significant difference in HbA1c levels. The authors reported similar HbA1c levels between baseline and 24 months and also between 24 and 60 months and suggested that T1DM or T2DM may not have a significant effect on periodontal treatment outcomes provided that the patients perform good plaque control. On the other hand, better glycaemic control was reported in T1DM patients ($n=14$) than T2DM patients ($n=27$) with non-surgical periodontal treatment and 6-month follow-up [55].

Skaleric et al. [56] compared scaling and root planing (SRP) alone and SRP + local application of an antimicrobial in poorly controlled T1DM patients (HbA1c ≥ 9%) and reported similar effects in both treatment groups. This study lacked a systemically healthy control group, and the power was rather small with 20 diabetic individuals. Possible effects of an adjunctive systemic antibiotic on HbA1c levels were investigated in T1DM patients with 3-month follow-up [57]. The authors failed to detect any significant difference with adjunctive systemic doxycycline in HbA1c levels and suggested that insulin dose, diet, and exercise may have a role on the outcomes. In another study on 65 T1DM patients, systemic antibiotics in addition to non-surgical or surgical periodontal treatment resulted in successful resolution of periodontal inflammation and 0.1% decrease in HbA1c level from 8.6 to 8.5 with 8-month follow-up [58].

Another study compared the 3-month outcomes of non-surgical periodontal treatment in periodontitis patients with or without T1DM and reported no improvement in clinical periodontal parameters and HbA1c levels [59]. The authors concluded that the lack of detectable effect may be explained by the small sample size (20 patients in each group).

There are also studies reporting a negative effect on HbA1c levels with periodontal treatment although the differences were not significant statistically [60, 61]. According to a recent consensus report from a joint workshop of European Federation of Periodontology (EFP) and International Diabetes Federation (IDF) [19••], there is insufficient evidence about the effect of periodontal therapy on HbA1c reduction in people with T1DM due to paucity of studies and further exploration is required. Accordingly, data on adjunctive benefit of antibiotics among people with T1DM are insufficient.

Conclusion

According to the current literature, it is still unclear whether periodontal treatment improves metabolic control in T1DM, although 0.4% decrease in HbA1c has been documented for T2DM [Cairo 20,21]. Moreover, the nature of connection between T1DM and periodontitis has not been clarified yet. There are well-performed studies documenting a higher risk of periodontitis in children with T1DM. Quantitative

and qualitative salivary changes in diabetics have also been reported. A greater effect of periodontal treatment on HbA1c levels in T2DM patients compared to T1DM was reported in a meta-analysis [63]. The limited number of studies involving T1DM patients may have a role in this finding. Furthermore, another meta-analysis failed to detect a correlation between circulating inflammatory markers and T1DM [30] and the impact of periodontal inflammation on metabolic control in T1DM could not be verified.

Involvement of mainly children and adolescents in clinical studies on T1DM may be regarded as another likely explanation for the failure of detecting a significant relationship with periodontitis.

Future Studies

Larger scale, controlled, representative of the whole population, and preferentially longitudinal studies on T1DM patients with detailed parameters on both diabetes and periodontal disease are warranted to better clarify the interaction between T1DM and periodontitis. A closer collaboration between endocrinologists and periodontists may help to improve general well-being of population.

Declarations

This article has been reviewed by Prof. Olivier Huck, as Dr. Nurcan Buduneli is a Section Editor for the topical collection Systemic Diseases.

Conflict of Interest The author declares no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

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