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Reviews

Type 1 diabetes mellitus and host–bacterial interactions in the oral cavity

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Abstract

Type 1 diabetes mellitus (T1DM) is an autoimmune disease which is characterized by the destruction of insulin-producing pancreatic β-cells. Current evidence supports the contribution of T-cells, macrophages, B-cells, and dendritic cells to the pathogenesis of T1DM as well. T1DM-associated risk factors, including defects in host immune response, socioeconomic conditions, and environmental factors create a dysbiotic environment in the oral cavity, which support the growth of pathogenic microbial biofilms. Changes in microbial composition, together with the diminished immune response, lead to the development of two most common oral diseases, caries and periodontal diseases. In the present review, we summarized the current evidence on oral manifestations of T1DM and described the shifts in oral microbial composition and oral immune response.

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Introduction

Type 1 diabetes mellitus (T1DM) is the most prevalent form of diabetes in children and adolescents. The disease is characterized by the destruction of pancreatic β-cells, insulin deficiency, and hyperglycemia. The destruction of β-cells has autoimmune character with combined influence of genetic (primarily at the HLA loci) and environmental factors. T-cells have a major role in the autoimmune destruction of pancreatic β-cells and the aggregated interleukin (IL)-17 response is seen as a hallmark of T1DM [1].

The acquisition of the oral microbiome begins at birth, with the mode of delivery being the first determinant of its composition. Once established, the interplay between the host immune system and the environment continues to shape the microbial community in the mouth [2]. This short review will focus on oral microbiome in T1DM patients and its relation to infectious diseases of the oral cavity. While doing that, we will briefly discuss the shifts in the oral immune response that may shape the oral microbial composition in T1DM patients.

Teeth, periodontium, and oral bacteria

In the oral cavity, teeth are surrounded by periodontium, i.e. root cementum, periodontal ligament, alveolar bone, and gingiva. Periodontium supports the teeth and shields nerves and blood vessels from mechanical loading. It is a dynamic organ with the ability to regenerate, and its innate and acquired immune mechanisms protect the oral cavity from oral pathogen invasion [3].

The oral cavity hosts a diverse microbiota with over 700 bacterial species. In the healthy oral cavity, there is well-organized homeostasis between different bacterial species and the host. This relation is primarily symbiotic and fosters numerous positive effects on oral health [4]. The symbiosis supports host defense functions, confers resistance to pathogen colonization, and suppresses the adherence of harmful species to the mucosa. Additionally, it exhibits antioxidant and anti-inflammatory properties, provides metabolic potential, contributes to a healthy digestive tract, and regulates the cardiovascular system [5]. Disruption of this balance can lead to microbial dysbiosis, contributing to various oral and systemic diseases [6].

Major infectious diseases of the oral cavity

Dental caries and periodontal diseases are the most common infectious diseases of the oral cavity. Dental caries is a biofilm-mediated disease that leads to mineral loss in dental hard tissues [7]. If untreated, it can progress to pulp infection, pulp necrosis, and tooth loss [8]. Periodontal diseases include gingivitis and periodontitis, which are inflammatory responses against oral infection. Periodontal diseases are common globally, the prevalence of mild and moderate forms of periodontitis is about 50% and the severe disease is about 10% [9].

Periodontal diseases are caused by biofilm components derived from microbial plaque accumulating at the gingival sulcus. Bacterial irritation of the periodontal tissues leads to a defensive reaction, and various inflammatory mediators are released in the gingiva, attracting the body's defense cells to destroy the bacteria. As a result, increase in vascularization, vascular permeability, and inflammatory cell numbers in gingiva cause swelling, redness, and bleeding, i.e. gingivitis [10]. Periodontitis is the result of a long-term inflammatory reaction in a susceptible host. The immune response against bacterial infection leads to the degradation of the periodontium. Pathogens associated with periodontitis play a crucial role in triggering the inflammatory cascade and the disease. As a consequence of the body's defense reaction, the collagen component of periodontium undergoes degradation, and the junctional epithelium of the dental sulcus migrates apically leading to the formation of pathological, deep pockets around the teeth. When osteoclastogenesis is activated, alveolar bone becomes progressively destroyed. The bone destruction is irreversible and can eventually lead to tooth loss. Additionally, periodontitis contributes to systemic inflammation and bacteremia, influencing the initiation or development of various systemic diseases [9].

Oral clinical changes in T1DM

Numerous studies indicated the oral manifestations of T1DM. The intraoral changes in T1DM are often associated with neuropathy, longer duration of diabetes, and poor glycemic control [11–13]. For example, patients with T1DM and neuropathy commonly have decreased salivary flow rates. Indeed, a recent meta-analysis concluded that T1DM patients have decreased salivary flow rate than healthy individuals [12]. Burning mouth syndrome is also linked secondarily to diabetes, poor glycemic control, and diabetic neuropathy [13]. Furthermore, T1DM patients are more prone to develop oral infectious diseases with tissue-degradative character, i.e. caries and periodontal disease [14–16]. Reduced salivary flow, which is a common phenomenon in T1DM patients, decreases the salivary buffer and remineralization capacities and increases the tendency to develop caries lesions and gingivitis [14]. In addition, as a metabolic disorder, T1DM can affect mineralized tissue structure, impair the formation of enamel and dentine, and reduces craniofacial growth, resulting in retardation of skeletal development [15]. Finally, diabetes exacerbates the susceptibility to develop periodontal diseases, and the severity of the effect is highly dependent on glycemic control [16].

Oral immunological shifts in T1DM

Recent studies indicated that it is not only T-cells that take part in development of T1DM, but also macrophages, B-cells, and dendritic cells play significant role in destruction of pancreatic β-cells [17]. Upregulated Th17 immunity in peripheral blood T cells [18] and elevated serum T-cell cytokine and macrophage activation-related chemokine levels were observed [19,20] in T1DM patients. Overall, these findings indicate a possible systemic disturbance in T-cell and macrophage responses in this group of patients. While the oral immune response is highly regulated by the oral microbiota and resident cells of periodontium, it is still part of the systemic immune response. Consequently, systemic disorders characterized by dysregulations in immune response disturb the oral immune response as well. Likewise, elevated salivary monocyte chemoattractant protein (MCP)-1, MCP-3, monokine induced by interferon gamma (MIG), macrophage inflammatory protein (MIP)-1α [21], immunoglobulin-G (IgG) [22], and S100 calcium-binding protein A9 (S100A9) [23] have been observed in T1DM patients. Moreover, decreased gingival tissue IL-10, osteoprogerin (OPG) [24], salivary glutathione [25], and salivary human β-defensin-3 (hBD-3) [26] levels were also detected in T1DM patients. Elevated salivary macrophage (MCP-1, MCP-3, MIP-1α, and S100A9) and T-cell (MIG) activation-related chemokines in T1DM patients indicate that these groups of patients have predisposition to inflammatory diseases, which is probably related to systemic macrophage and T-cell disturbance. On the other hand, decreased levels of anti-inflammatory (IL-10), anti-oxidative (glutathione), anti-microbial (hBD-3), and anti-osteoclastogenesis (OPG) mediators suggest deficiencies in the protective mechanisms of oral cavity in T1DM patients. Taken together, these factors may explain why T1DM patients have a higher tendency to develop infection-induced inflammatory diseases.

Oral bacterial colonization and virulence in T1DM

In contrast to the high number of studies evaluating the oral bacterial composition in T2DM patients, the number of studies describing the oral microbial composition of T1DM patients is highly limited. Table 1 summarizes the findings of the recent studies exploring oral microbial composition and virulence in T1DM patients [27–38].

While the population characteristics of these studies are heterogeneous, the microbial compositions of T1DM patients have a tendency towards cariogenic and

Table 1

Summary of the recent studies exploring oral microbial composition in T1DM patients.

Article	Aim	Study material	Study groups	Main findings
Carelli et al., 2023 [27]	To evaluate the interplay between bacteria composition, oral hygiene, and glycemic control in a cohort of children with T1DM	Saliva	Age range: 9−15 years. Group: T1DM patients, n = 89.	In T1DM patients, glycemic control and regular oral hygiene regulate the establishment of oral microbiota predisposing to dental and periodontal pathology.
Yuan et al., 2022 [39]	To delineate the community structure of the oral microbiome in T1DM children in both the acute and chronic phases and to explore the association with systemic metabolic status	Saliva	Age range: 4.5−14 years. Group 1: Healthy children, n = 47. Group 2: Children with new-onset T1DM. Group 3: Children with T1DM in the chronic phase receiving insulin treatment.	The acute phase of T1DM was characterized by oral microbiota dysbiosis, which could be partially ameliorated with insulin therapy, indicating that glycemic control may enhance oral microbiota disturbance and oral complications.
Selway et al., 2023 [28]	To determine if there is an association between hyperlipidemia, periodontal disease, and the oral microbiota of children with T1D, as this has not yet been explored.	Gingival swab	Age range: 12.9 ± 2.5 years. Group: T1DM patients, n = 72	Findings support an association between oral microbiota and two different exposure variables: familial history of hyperlipidemia and periodontal risk factors.
Ferizi et al., 2022 [29]	To analyze the impact of metabolic control on saliva, dental caries, dental plaque, gingival inflammation, and cariogenic bacteria in saliva	Saliva	Age range: 10−15 years. Group 1: T1DM with good metabolic control (HbA1c < 7.5%), n = 34. Group 2: T1DM with poor metabolic control (HbA1c > 7.5%), n = 46.	Higher values of *Streptococcus mutans* and *Lactobacillus* colonies in poorly controlled T1DM group.
Chakraborty et al., 2021 [30]	To identify oral microorganisms and assess oral biofilm in children & adolescents with T1DM and Periodontal disease	Gingival plaque	Age range: 10−18 years. Group 1: T1DM with periodontal disease, n = 20. Group 2: T1DM without periodontal disease, n = 20. Group 3: Periodontal disease without T1DM, n = 20.	T1DM with worse glycaemic control, associated with higher abundance of biofilm formation and greater microbial diversity, especially in those with T1DM with PD.
Jensen et al., 2021 [31]	To characterize the diversity and composition of oral microbiota in children with T1DM.	Buccal and gingival swab	Age range: 13.3 ± 2.6 years. Group: T1DM, n = 77.	HbA1c was associated with changes to the diversity and composition of the oral micro-biota,
Moskovitz et al., 2021 [32]	To characterize the oral microbiome associated with T1D in children after the onset of the disease	Unstimulated saliva	Age range: 5−15 years. Group 1: T1DM patients, n = 37. Group 2: Healthy controls, n = 29.	Salivary microbiome analysis revealed unique microbial taxa that differed between T1D children and healthy subjects. Several genera found in the saliva of T1D children were associated with gut microbiome in T1D individuals.
Babatzia et al., 2020 [33]	To study the oral health of young individuals with controlled and uncontrolled T1DM and compare the results with those for healthy counterparts.	Stimulated saliva	Age range: 6−15 years. Group 1: Poorly controlled T1DM, n = 35. Group 2: Well-controlled T1DM, n = 39. Group 3: Healthy controls, n = 70.	Candida levels were not different among groups. *Strep. mutans* was higher in poorly controlled T1DM compared to healthy controls.

(*continued on next page*)

Table 1. (*continued*)

Article	Aim	Study material	Study groups	Main findings
Mahalakshmi et al., 2019 [34]	To compare and assess the risk of periodontitis due to the carriage of *Eikenella corrodens*, *Campylobacter rectus*, *Prevotella intermedia* and *Prevotella nigrescens*.	Subgingival plaque	Age range: 7–14 years. Group 1: T1DM patients, n = 50. Group 2: Healthy controls, n = 50.	Significant difference was not observed for the prevalence of all the four periodontal pathogens between type 1 diabetic and healthy children
Costa et al., 2017 [35]	To evaluate the yeast oral carriage (in saliva and mucosal surface) of children with T1DM and potential relation with host factors, particularly the subset of CD4+ T cells.	Stimulated saliva and cheek mucosal swabs	Age range: 5–15 years. Group 1: T1DM patients, n = 133. Group 2: Healthy controls, n = 72.	The presence of yeasts in the oral cavity was not affected by diabetes, metabolic control or duration of the disease.
Duque et al., 2017 [36]	To compare the prevalence of periodontal pathogens, systemic inflammatory mediators and lipid profiles in type 1 diabetes children (DM) with those observed in children without diabetes (NDM), both with gingivitis.	Subgingival plaque	Age range: 9.52 ± 1.86 years (T1DM) and 9.45 ± 1.69 years (control). Group 1: T1DM patients, n = 24. Group 2: Healthy controls, n = 27.	The presence of *Capnocytophaga sputigena* and *Capnocytophaga ochracea* were associated with gingivitis in DM children.
Merchant et al., 2016 [37]	To evaluate the association between periodontal microorganism groups and early markers of CVD in youth with t1DM.	Subgingival plaque 41 periodontal microorganisms	Age range: 12–19 years. Group 1: T1DM patients, n = 105. Group 2: Healthy controls, n = 71.	HbA1c was inversely associated with yellow/other cluster among youth with t1DM. HbA1c was not associated with periodontal microorganism clusters among youth without diabetes.
Lalla et al., 2006 [38]	To investigate the levels of subgingival plaque bacteria in patients with type 1 diabetes and non-diabetic controls of comparable periodontal status.	Plaque	Age range: 6–41 years Group 1: T1DM patients, n = 50. Group 2: Healthy controls, n = 50	*Eubacterium nodatum* levels were higher in diabetic patients.

periodontopathogenic profile. In salivary samples of T1DM patients, high prevalence of *Actinomyces* spp., *Lactobacillus* spp., *Veillonella* spp., *Streptococcus mutans*, *Treponema denticola*, *Agregatibacter actinomycetemcomitans* and *Prevotella intermedia* were detected [27]. Moreover, prevalence of *S. mutans* [27,33], *Veillonella* spp. [27], and *Lactobacillus* [29] were significantly related to poor glycemic control. Besides, T1DM patients had less salivary microbial diversity in comparison to systemically healthy children, and *Granulcatella-unclassified*, *Mogibacterium-unclassified*, *Alloprevotella rava*, *Catonella morbi*, *Fusobacterium periodonticum*, *Oribacterium parvum*, *Prevotella melaninogenica*, and *Prevotella pallens* were found at higher values among systemically healthy children than in T1DM patients [32]. Decreased microbial diversity in T1DM patients was later confirmed by Yuan et al. [39]. Their study also showed increased abundance of genera harboring opportunistic pathogens, such as *Streptococcus*, *Rothia* and *Rhodococcus* in children with acute phase of T1DM [39]. Interestingly, in the same study, the group that received insulin treatment demonstrated partial recovery from oral microbial dysbiosis, which indicated that adequate metabolic control may decelerate the proliferation of pathogenic bacteria [39]. Moskovitz et al. [32] described the identification of several unique taxa in children with T1DM, including *Lactobacillus salivarius*, *Ruminococcus bromii*, *Prevotella copri*, *Ruminococcus champanellensis*, and *Faecalibacterium prausnitzii*, and they related this outcome to poor quality diet consumption of children with T1DM. After all, it is possible that environmental factors, especially fermentable carbohydrate-rich poor diet, explain the association between T1DM and pro-cariogenic bacterial colonization [27].

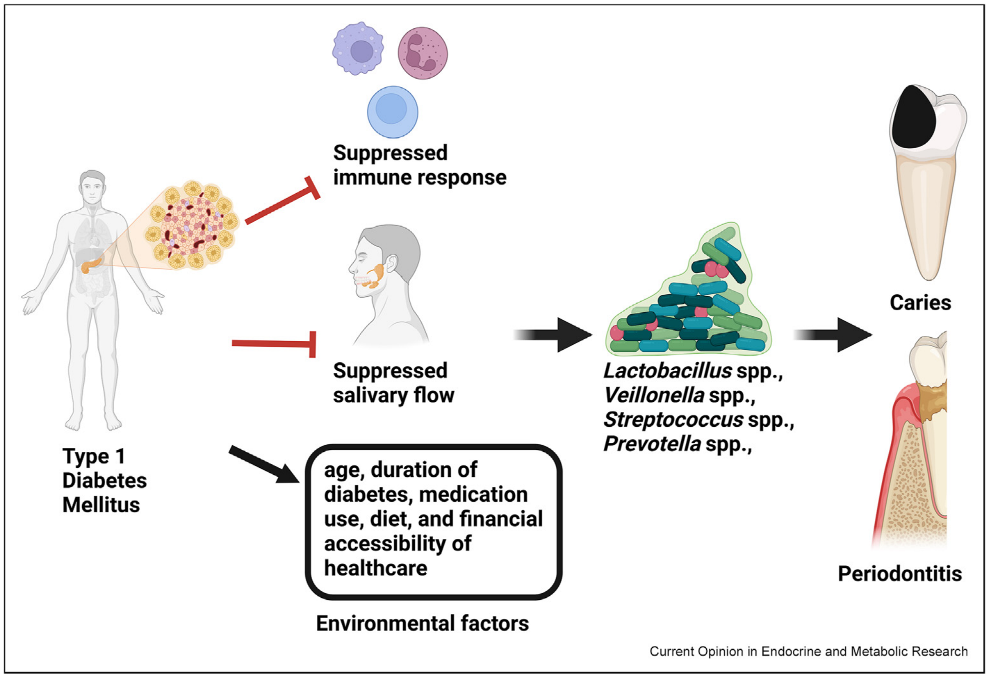
When dental plaque samples were analyzed with culture-based methods, *Staphylococcus milleri*, *Streptococcus mitis*, and *Enterococcus faecalis* were identified more frequently in T1DM patients than in systemically healthy controls [30]. When the subgingival samples were analyzed by checkerboard DNA–DNA hybridization using whole genomic probe for 12 periodontitis-associated bacteria, the only difference was observed in the colonization of *Eubacterium nodatum*, which was elevated in T1DM patients [38]. In the same study, no statistical difference was observed between T1DM patients and systemically healthy controls when their serum IgG antibodies against 12 tested bacterial species were compared. Indeed, infection ratio analysis revealed similar levels of responsiveness to periodontal bacteria in T1DM patients and systemically healthy controls [38]. PCR-based analyses indicated higher levels of *Capnocytophaga sputigena* and *Capnocytophaga ochracea* in subgingival biofilm samples of children with T1DM [36], while no difference was observed in prevalence of *Eikenella corrodens*, *Campylobacter rectus*, *Prevotella intermedia*, and *Prevotella nigrescens* [34]. In the plaque samples of T1DM patients, an inverse association was observed between serum glycated hemoglobin (HbA1c) levels and the presence of microorganisms that are not related to periodontitis [37]. Nevertheless, the complexity of microbiota was associated with HbA1C levels of T1DM patients [31]. However, in the same study, a similar association was not observed when the buccal mucosa samples were analyzed for their microbial complexity, indicating that the localization of the biofilm sampling site has utmost importance in the outcome of microbiota studies [31]. In line with these findings, a recent study concluded that the oral microbiota of T1DM patients cannot be treated as one large, homogenous bacterial ecosystem. The microbial composition in particular niches of the oral cavity is significantly different [40]. Oral *Prevotella* abundance in gingival plaque swab samples was also related to the familial history of hyperlipidemia in children with T1DM [28]. When the oral yeast colonization was evaluated, *Candida albicans* was the most predominant yeast specie in oral mucosal swab (30.8%) and saliva (46.6%) samples of T1DM children [35]. Moreover, yeast salivary biodiversity was related to systemic health. Overall, no difference was observed between T1DM children and systemically healthy controls in terms of their yeast colonization [35].

Summary and conclusion

According to the current evidence, T1DM patients have tendency to develop more cariogenic and periodontopathogenic microbiomes. *Lactobacillus* spp., *Veillonella* spp., *Streptococcus* spp., and *Prevotella* spp., are the most common group of oral bacteria that are isolated from T1DM patients. Oral *Lactobacillus*, *Streptococcus*, *and Prevotella* species are commensals that are commonly found in the oral cavity with the ability to adapt to environmental stresses, including changes in energy sources and oxidative stress, and pH. *Veillonella* species on the other hand are asaccharolytic. However, it can utilize lactate, pyruvate, and oxaloacetate as energy sources and produce H_2S. Thus, increase in the prevalence of these bacteria may directly relate to the caries lesions, and indirectly create a suitable environment for the growth of periodontitis-associated pathogenic biofilms. There is also evidence that the oral host response is diminished in T1DM patients; however, this phenomenon does not seem relate to the oral microbiota, but may be related to the impaired systemic immune response. It is also evident that glycemic control has a major role in oral microbial composition. The second important regulator seems to be diet, which may directly or indirectly affect the immune response of the host (Figure 1).

The heterogeneity of the published studies was the main limitation of this review. It has been shown that

Figure 1



Risk factors that connect common oral infectious diseases (i.e. caries and periodontitis) with Type 1 Diabetes Mellitus (Created with BioRender.com).

age, duration of diabetes, medication use, diet, and financial accessibility of healthcare determine not only oral microbial composition but also host immune response. Therefore, there is significant need of well-designed large-scale studies to derive valid conclusions.

CRediT author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. * Majumdar S, Lin Y, Bettini ML: **Host-microbiota interactions shaping T-cell response and tolerance in type 1 diabetes**. *Front Immunol* 2022, **13**, 974178.
An in-depth review of the immune response disturbance in type 1 diabetes mellitus. Review especially brings the gut-thymus and gut-pancreas communications in the explanation of type 1 diabetes mellitus pathogenesis.

2. * Sedghi L, DiMassa V, Harrington A, Lynch SV, Kapila YL: **The oral microbiome: role of key organisms and complex networks in oral health and disease**. *Periodontol 2000* 2021, **87**:107–131.
An extensive review describing the symbiotic relations between oral microbiota and oral tissues.

3. Bartold PM, McCulloch CA: **Information generation and processing systems that regulate periodontal structure and function**. *Periodontol 2000* 2013, **63**:7–13.

4. Abdulkareem AA, Al-Taweel FB, Al-Sharqi AJB, Gul SS, Sha A, Chapple ILC: **Current concepts in the pathogenesis of periodontitis: from symbiosis to dysbiosis**. *J Oral Microbiol* 2023, **15**, 2197779.

5. Kilian M, Chapple ILC, Hannig M, Marsh PD, Meuric V, Pedersen AML, Tonetti MS, Wade WG, Zaura E: **The oral**

microbiome–an update for oral healthcare professionals. *Br Dent J* 2016, **221**:657–666.

6. Maier T: **Oral microbiome in health and disease: maintaining a healthy, balanced ecosystem and reversing dysbiosis**. *Microorganisms* 2023, **11**:1453.

7. Machiulskiene V, Campus G, Carvalho JC, Dige I, Ekstrand KR, Jablonski-Momeni A, Maltz M, Manton DJ: **Terminology of dental caries and dental caries management: consensus report of a workshop organized by ORCA and Cariology Research Group of IADR**. *Caries Res* 2020, **54**:7–14.

8. Bjørndal L, Simon S, Tomson PL, Duncan HF: **Management of deep caries and the exposed pulp**. *Int Endod J* 2019, **52**:949–973.

9. Könönen E, Gursoy M, Gursoy UK: **Periodontitis: a multifaceted disease of tooth-supporting tissues**. *J Clin Med* 2019, **8**:1135.

10. Trombelli L, Farina R, Silva CO, Tatakis DN: **Plaque-induced gingivitis: case definition and diagnostic considerations**. *J Clin Periodontol* 2018, **45**:44–67.

11. Duda-Sobczak A, Zozulinska-Ziolkiewicz D, Wyganowska-Swiatkowska M: **Type 1 diabetes and periodontal health**. *Clin Ther* 2018, **40**:823–827.

12. Hatipoğlu Ö, Önsüren AS, Hatipoğlu FP, Kurt A: **Caries-related salivary parameters and oral microbial flora in patients with type 1 diabetes: a meta-analysis**. *Diabetes Metab Res Rev* 2022, **38**, e3527.

13. Moore PA, Guggenheimer J, Orchard TJ: **Burning mouth syndrome and peripheral neuropathy in patients with type 1 diabetes mellitus**. *Diabetes Complications* 2007, **21**:397–402.

14. ** Genco RJ, Borgnakke WS: **Diabetes as a potential risk for periodontitis: association studies**. *Periodontol 2000* 2020, **83**: 40–45.

An important review to describe the underlying association between diabetes and periodontitis.

15. Abbassy MA, Watari I, Soma K: **Effect of experimental diabetes on craniofacial growth in rats**. *Arch Oral Biol* 2008, **53**: 819–825.

16. Graves DT, Ding Z, Yang Y: **The impact of diabetes on periodontal diseases**. *Periodontol 2000* 2020, **82**:214–224.

17. Roep BO, Thomaidou S, van Tienhoven R, Zaldumbide A: **Type 1 diabetes mellitus as a disease of the β-cell (do not blame the immune system?)**. *Nat Rev Endocrinol* 2021, **17**:150–161.

18. Honkanen J, Nieminen JK, Gao R, Luopajarvi K, Salo HM, Ilonen J, Knip M, Otonkoski T, Vaarala O: **IL-17 immunity in human type 1 diabetes**. *J Immunol* 2010, **185**:1959–1967.

19. Antonelli A, Fallahi P, Ferrari SM, Pupilli C, d'Annunzio G, Lorini R, Vanelli M, Ferrannini E: **Serum Th1 (CXCL10) and Th2 (CCL2) chemokine levels in children with newly diagnosed Type 1 diabetes: a longitudinal study**. *Diabet Med* 2008, **25**: 1349–1353.

20. Ismail NA, Abd El Baky AN, Ragab S, Hamed M, Hashish MA, Shehata A: **Monocyte chemoattractant protein 1 and macrophage migration inhibitory factor in children with type 1 diabetes**. *J Pediatr Endocrinol Metab* 2016, **29**:641–645.

21. Yilmaz N, Polat R, Gürsoy M, Kaman W, Gül Aydin E, Fteita D, Yilmaz D, Bikker F, Gürsoy UK: **Salivary macrophage activation-related chemokines and mitogen-activated kinase kinase-degrading proteolytic activity in type 1 diabetes mellitus**. *J Periodontol* 2023, **94**:896–904.

22. Javed F, Sundin U, Altamash M, Klinge B, Engström PE: **Self-perceived oral health and salivary proteins in children with type 1 diabetes**. *J Oral Rehabil* 2009, **36**:39–44.

23. Cabras T, Pisano E, Mastinu A, Denotti G, Pusceddu PP, Inzitari R, Fanali C, Nemolato S, Castagnola M, Messana I: **Alterations of the salivary secretory peptidome profile in children affected by type 1 diabetes**. *Mol Cell Proteomics* 2010, **9**: 2099–2108.

24. Duarte PM, Neto JB, Casati MZ, Sallum EA, Nociti Jr FH: **Diabetes modulates gene expression in the gingival tissues of patients with chronic periodontitis**. *Oral Dis* 2007, **13**:594–599.

25. Gümüş P, Buduneli N, Cetinkalp S, Hawkins SI, Renaud D, Kinane DF, Scott DA: **Salivary antioxidants in patients with type 1 or 2 diabetes and inflammatory periodontal disease: a case-control study**. *J Periodontol* 2009, **80**:1440–1446.

26. Yilmaz D, Yilmaz N, Polat R, Nissilä V, Aydõn EG, Rautava J, Gürsoy M, Gürsoy UK: **Salivary levels of hBDs in children and adolescents with type 1 diabetes mellitus and gingivitis**. *Clin Oral Investig* 2022, **26**:4897–4904.

27. Carelli M, Maguolo A, Zusi C, Olivieri F, Emiliani F, De Grandi G, Unali I, Zerman N, Signoretto C, Maffeis C: **Oral microbiota in children and adolescents with type 1 diabetes mellitus: novel insights into the pathogenesis of dental and periodontal disease**. *Microorganisms* 2023, **11**:668.

28. Selway CA, Jensen ED, Pena AA, Smart G, Weyrich LS: **Type 1 diabetes, periodontal health, and a familial history of hyperlipidaemia is associated with oral microbiota in children: a cross-sectional study**. *BMC Oral Health* 2023, **23**:15.

29. Ferizi L, Bimbashi V, Kelmendi J: **Association between metabolic control and oral health in children with type 1 diabetes mellitus**. *BMC Oral Health* 2022, **22**:502.

30. Chakraborty P, Chowdhury R, Bhakta A, Mukhopahyay P, Ghosh S: **Microbiology of periodontal disease in adolescents with type 1 diabetes**. *Diabetes Metab Syndr* 2021, **15**, 102333.

31. Jensen ED, Selway CA, Allen G, Bednarz J, Weyrich LS, Gue S, Peña AS, Couper J: **Early markers of periodontal disease and altered oral microbiota are associated with glycemic control in children with type 1 diabetes**. *Pediatr Diabetes* 2021, **22**: 474–481.

32. Moskovitz M, Nassar M, Moriel N, Cher A, Faibis S, Ram D, Zangen D, Yassour M, Steinberg D: **Characterization of the oral microbiome among children with type 1 diabetes compared with healthy children**. *Front Microbiol* 2021, **12**, 756808.

33. Babatzia A, Papaioannou W, Stavropoulou A, Pandis N, Kanaka-Gantenbein C, Papagiannoulis L, Gizani S: **Clinical and microbial oral health status in children and adolescents with type 1 diabetes mellitus**. *Int Dent J* 2020, **70**:136–144.

34. Mahalakshmi K, Arangannal P, Santoshkumari: **Frequency of putative periodontal pathogens among type 1 diabetes mellitus: a case-control study**. *BMC Res Notes* 2019, **12**:328.

35. Costa AL, Silva BMA, Soares R, Mota D, Alves V, Mirante A, Ramos JC, Maló de Abreu J, Santos-Rosa M, Caramelo F, Gonçalves T: **Type 1 diabetes in children is not a predisposing factor for oral yeast colonization**. *Med Mycol* 2017, **55**:358–367.

36. Duque C, João MF, Camargo GA, Teixeira GS, Machado TS, Azevedo RS, Mariano FS, Colombo NH, Vizoto NL, Mattos-Graner RO: **Microbiological, lipid and immunological profiles in children with gingivitis and type 1 diabetes mellitus**. *J Appl Oral Sci* 2017, **25**:217–226.

37. Merchant AT, Nahhas GJ, Wadwa RP, Zhang J, Tang Y, Johnson LR, Maahs DM, Bishop F, Teles R, Morrato EH: **Periodontal microorganisms and cardiovascular risk markers in youth with type 1 diabetes and without diabetes**. *J Periodontol* 2016, **87**:376–384.

38. * Lalla E, Kaplan S, Chang SM, Roth GA, Celenti R, Hinckley K, Greenberg E, Papapanou PN: **Periodontal infection profiles in type 1 diabetes**. *J Clin Periodontol* 2006, **33**:855–862.

A comprehensive study to oral bacteria-systemic immunoglobulin response interactions in type 1 diabetes mellitus patients

39. * Yuan X, Wu J, Chen R, Chen Z, Su Z, Ni J, Zhang M, Sun C, Zhang F, Liu Y, He J, Zhang L, Luo F, Wang R: **Characterization of the oral microbiome of children with type 1 diabetes in the acute and chronic phases**. *J Oral Microbiol* 2022, **14**, 2094048.

The results of this study is unique as it describes the oral microbiome of type 1 diabetes mellitus in regard to diabetes activity.

40. Gregorczyk-Maga I, Fiema M, Kania M, Jachowicz-Matczak E, Romaniszyn D, Gerreth K, Klupa T, Wójkowska-Mach J: **Oral microbiota—one habitat or diverse niches? A pilot study of sampling and identification of oral bacterial and fungal biota in patients with type I diabetes mellitus treated with insulin pump**. *Int J Environ Res Public Health* 2023, **20**:2252.