



Gingivitis and periodontitis in children and adolescents suffering from type 1 diabetes mellitus

Gingivitis i parodontopatija kod dece i adolescenata obolelih od dijabetesa melitusa tipa 1

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Introduction

Type 1 diabetes mellitus (DM) is a systemic disease which causes a number of complications which reduce the quality of life of the affected individuals. Gingivitis and periodontitis are local inflammatory diseases of the supporting tooth structures (periodontium) which can have an influence on other organs and organic systems. The Expert Group Report on Diagnosis and Classification of Diabetes¹ included periodontitis as one of the pathological conditions which often occur in adults with DM. However, it has not yet been defined whether patients with DM are likely to develop periodontitis, or if periodontitis leads to the exacerbation of DM. Although, there are many data indicating the correlation between periodontitis and type 1 DM in children and adults, the influence of the level of glycaemic control on the condition of periodontium is still not entirely clear. Additionally, the quantitative status of immunological markers in saliva in these two diseases is unknown.

The aim of this paper was to present clinical studies dealing with the biochemical processes in saliva and other bodily fluids, which could elucidate the relationship between gingivitis and periodontitis, on the one hand, and type 1 DM, on the other.

The literature data on the correlation between gingivitis/periodontitis and type 1 DM were collected in the period from 1968 to September 2011 using the PubMed and Medline data bases and 59 studies were selected for this paper.

The analysis encompassed original papers, review articles and scientific and expert meetings reports. All selected studies were published in English language. The analysis did not include: case reports, letters to the editors, short announcements, studies with inadequate methodology and incomplete or unrelated articles. The following key words were used for the electronic search in the MeSH browser: periodontitis, gingivitis, type 1 diabetes mellitus, cytokines, interleukin-8 and saliva.

A summary table was created with data including the authors' name, the year of publication of the study, the duration of type 1 DM, the monitored biochemical and clinical parameters and the conclusion based on the examined articles (Addendum 1).

Type 1 diabetes mellitus

Type 1 DM is primarily found in children and adolescents and makes up 5–10% of the total number of patients with both types of diabetes². The pathological basis of type 1 DM is the autoimmune destruction of pancreatic islets' β -cells resulting in a marked or complete loss of insulin secretion resulting in hyperglycemia. Various types of molecular markers of autoimmune β -cells destruction can be detected in 85–90% of patients with hyperglycemia². Some of them, such as autoantibodies against insulin, glutamic acid decarboxylase and tyrosine phosphatases, are used for the diagnosis and risk assessment of developing type 1 DM³. Compli-

cations of type 1 DM are retinopathy with a possible loss of sight, nephropathy which leads to renal failure, peripheral neuropathy with a risk of ulcerations and amputation of the lower extremities and autonomic neuropathy causing gastrointestinal, genitourinary and cardiovascular diseases. Atherosclerosis, cardiovascular, peripheral arterial and cerebrovascular diseases are more often present in patients with diabetes mellitus². In addition to these, accompanying skin lesions were examined in children with type 1 DM⁴. Furthermore, in 1993, periodontitis was identified as one of the classic complications of DM⁵. An important indicator of general condition and possible diabetes complications is metabolic control, which is monitored through the blood glucose level (BGL) and glycosylated hemoglobin level (HbA1c). In healthy individuals, the proportion of HbA1c ranges between 4% and 6% of total hemoglobin, while in the hyperglycaemic it can reach 15%. Since HbA1c remains stable for several months after the occurrence of hyperglycaemia, it serves as a marker of the severity of DM or the efficacy of metabolic control during a certain period of time. The treatment of DM is aimed at normalising the blood glucose levels and reducing the HbA1c level to less than 7.5%⁶.

Gingivitis and periodontitis

Gingivitis and periodontitis are localised infections of the periodontium, which consists of the gingiva, the periodontal membrane, the root cementum and the alveolar bone. Gingivitis is an inflammation which affects only the gingiva, whereas periodontitis is an inflammation of the deeper periodontal tissues. Both diseases result from the interaction between periodontal pathogenic microorganisms and host tissues. Periodontal pathogens consist the bulk of the soft (dental biofilm) and solid (dental calculus) deposits on teeth. Dental biofilm is a colony of microorganisms which spontaneously and progressively accumulate on all solid surfaces in the mouth, primarily on teeth. Although this accumulation is spontaneous, many local factors can facilitate it. Gingivitis is initiated by the presence of periodontal pathogenic microorganisms which cause the disease, but the host response to the infection is critical for disease progression. Various systemic factors can influence this response. The clinical course of the advanced periodontitis does not differ in relation to the type of periodontal bacteria which induce the immune-mediated destructive processes⁷. When dental biofilm is present gingiva becomes red, enlarged, and bleeds easily when probed. Further expansion of the inflammatory process into the deeper periodontal tissues leads to the apical migration of the epithelial attachment resulting in the periodontal pocket, which is a pathognomonic sign of periodontitis. Unless the process is arrested by treatment, it will lead to alveolar bone resorption, which ultimately causes tooth loss. It was previously thought that gingivitis, if left untreated, will progress into periodontitis. However, gingivitis and periodontitis are two different pathological entities and although periodontitis is preceded by gingivitis, not all cases of gingivitis will progress to periodontitis. So far, it is not completely clear why and how gingivitis progresses to periodontitis.

Besides oral implications, periodontitis has an influence on systemic health. Systemic inflammation was more pronounced in patients with periodontitis as detected by the increased level of various serum inflammatory markers compared to the healthy controls⁸. Also, depending on the degree of the host response during periodontitis, various inflammatory biomarkers can be detected in samples of gingival crevicular fluid and saliva. Some of these molecules can influence gene expression in individuals with genetic polymorphism with the tendency to develop periodontitis⁹. These molecules can be used as diagnostic markers and tests and methods of assessing the risk of periodontitis by measuring the level of biomarkers are constantly being improved.

The correlation between diabetes mellitus and gingivitis/periodontitis

Diabetes and gingivitis/periodontitis are widespread chronic diseases. Their pathogenetic mechanisms are believed to be interrelated and many authors have proposed the mechanisms to explain their correlation. These common mechanisms can be attributed to the following factors: microvascular disease, changes in the composition of the gingival crevicular fluid, changes in collagen metabolism, altered host response, increased presence of periodontal pathogenic microorganisms, genetic predisposition and non-enzymatic glycosylation. Generally, in order to confirm the relationship between DM and gingivitis/periodontitis biologically plausible mechanisms must exist underlying the pathological interactions. These mechanisms are very similar to those of classic diabetic complications such as retinopathy, nephropathy, microvascular and macrovascular diseases and impaired wound healing.

Many studies indicate a higher incidence and severity of gingivitis and periodontitis in children and adolescents with type 1 DM compared to healthy children. According to Cianciola et al.¹⁰, severity and incidence of periodontal involvement was statistically more prominent in patients with type 1 DM and accompanying periodontitis compared to non-diabetic individuals of that age. In support to the above data, the results of Lalla et al.¹¹ and Daković and Pavlović¹² showed that gingival inflammation was significantly more common in children and adolescents with type 1 DM compared to the systemically healthy subjects of the same age group. Jenkins and Papapanou¹³ demonstrated that children with type 1 DM were in high risk of developing gingivitis, while the incidence of gingivitis in children and adolescents was almost double compared to adults. Some studies showed that severe forms of gingivitis were more frequent in children with type 1 DM compared to healthy children^{10, 14}, whereas other studies did not find this difference¹⁵.

The available literature data on the exclusive influence of dental biofilm on the development of gingivitis in patients with type 1 DM are controversial. In one study, the presence of gingivitis in children with type 1 DM was not related to higher dental biofilm accumulation, because a significant increase in plaque index (PI) was not found in this population¹⁶. Contrary to this, another study showed a significant

correlation between the presence of dental biofilm and gingivitis in children with type 1 DM compared to a healthy population¹³. In the research of Daković and Pavlović¹² the percentage of tooth sites with a gingival index (GI) higher than 2 was 18.3% in children with type 1 DM compared to 9.7% in healthy children, which is almost twice as high and with a high statistical significance ($p < 0.001$). This is in accordance with most authors who examined GI in this category of patients^{11, 14, 17, 18}. Additionally, the percentage of tooth sites where PI score was higher than 2 was significantly higher in children with type 1 DM compared to healthy children¹², which was in accordance with most authors^{11, 14, 16, 17}. Daković and Pavlović¹² also investigated the relationship between gingival bleeding and dental biofilm (the number of bleeding tooth sites compared to the number of biofilm covered tooth sites). The multivariate logistic regression analysis showed that periodontitis was in a positive correlation with GI and, more importantly, with bleeding/dental biofilm¹². Additionally, the increase in the relationship between bleeding and dental biofilm can identify the individuals inclined to develop periodontitis and be of great importance as a prognostic indicator of potential periodontitis¹⁹.

Several studies showed a positive correlation between glucose level and gingival inflammation. Hyperglycemia in children with a newly diagnosed DM was associated with a more severe form of gingival bleeding which is reduced by the improvement in glucose metabolism after the insulin therapy training. Children with poor metabolic control (average HbA1c = 15%) had a higher level of gingival bleeding compared to those with good or mild metabolic control²⁰. These children had a higher risk of developing a more severe form of periodontitis^{12, 17, 21}. Such findings in patients with type 1 DM can be explained by the fact that the excessive blood glucose, which enters the oral cavity through saliva and gingival crevicular fluid, soaks the biofilm and causes an increase in total biofilm accumulation. In children with poor metabolic control this mechanism can overwhelm the host defence against the dental biofilm and increase the risk of developing gingivitis. However, the reduction of hyperglycemia did not affect the clinical attachment level (CAL), probing pocket depth (PPD), gingival bleeding index (GBI) and PI¹². This can be explained by the fact that the improvement of glycaemic control in patients with type 1 DM can improve the periodontal parameters, but only if the patients adhere to proper oral hygiene measures.

It was found that pathological morphologic characteristics of capillaries in the gingiva and labial mucosa in patients with DM were more prominent compared to the healthy individuals²². Long-term hyperglycemia causes thinning of the basal membrane of vessel walls lining leading to the deterioration of tissue nourishment and leukocyte migration. This contributed to the concept of importance of the morphological and functional diabetic microvascular changes in the periodontium in patients with type 1 DM.

The values of clinical periodontal parameters in the subjects with type 1 DM¹² showed a better condition of their periodontium compared to the values of other authors in the same category^{11, 14, 17}. However, the incidence of periodonti-

tis was statistically higher in children suffering from DM, compared to healthy children. The ratio of periodontitis in healthy children was 7.9%, while in children with type 1 DM periodontitis was three times more common, i.e. 21.5%. Additionally, there was a higher presence of a more severe form of periodontitis, albeit statistically insignificant¹². The analysis of the effects of type 1 DM on the destruction of periodontal tissues showed some interesting results. Comparing CAL in diseased and healthy children a statistically significant difference was not found, but there was a significant difference in these two groups when the number of teeth and the number of tooth sites affected by periodontitis were compared¹². Type 1 DM was significantly correlated with the level of destruction of the periodontium regardless of the cut-off clinical parameter values used to define periodontitis¹². This information, as well as the results of other authors¹⁷, show that type 1 DM is a significant systemic factor which influences the development of periodontitis.

Numerous studies show that patients with DM and periodontitis have a higher risk of deterioration of glycaemic control over time compared to patients with DM alone²³. This is in accordance with the results of other authors who have found that children with type 1 DM and poor metabolic control had a higher risk of developing a more severe form of periodontitis^{12, 17, 21}. The influence of periodontal infection on the glycaemic control can be explained in several ways. The systemic inflammation following systemic infections, stimulates insulin resistance and affects the dynamics of glucose in the body²⁴. There is evidence that periodontitis, although a local disease, can stimulate or lead to a continuous increase in the systemic chronic inflammatory condition, reflected in the elevated level of serum C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen, especially in those harbouring Gram-negative periodontal pathogens (*Porphyromonas gingivalis*, *Tannerella forsythensis* and *Prevotella intermedia*)⁵. Bacteremia and endotoxemia, a result of the systemic dissemination of periodontal pathogens or their products, induce a systemic inflammatory disorder with an increase in the levels of serum inflammatory markers²⁵. One study showed that the level of endotoxin in blood was five times higher in patients with periodontitis compared to healthy individuals²⁶. The presence of periodontitis enables oral microorganisms and their products to reach systemic circulation²⁷.

Conversely, the mechanisms influencing the development of other complications of type 1 DM can also affect the pathogenesis of periodontitis²⁸. Some studies examining the correlation between type 1 DM and periodontitis are shown in Addendum 1. The results of these studies are difficult to compare due to a variety of clinical and laboratory protocols used. Besides, there is a certain number of studies which are not shown in Table 1 due to the obsolescence or inadequate presentation of clinical parameters. Namely, the parameters of gingival and periodontal health have recently been examined in more detail, whereas the percentage of the affected sites and the ratio between bleeding and dental biofilm were also examined in addition to GI and PI. Furthermore, special attention is paid to the parameters of periodontal destruction,

particularly to CAL, so that the term 'periodontal destruction' implies that there is at least one site with epithelial attachment loss larger than 1.5 mm (or 2 mm depending on the author) on two non-adjacent teeth. The duration of DM is an important risk factor for developing periodontitis. In young patients with type 1 DM periodontal tissue destruction starts relatively early, in pre-adolescent and adolescent period, depending on the duration of the underlying disease¹². Loss of epithelial attachment was more pronounced in patients suffering from type 1 DM longer than 10 years²⁹. On the same lines, the results of Lalla et al.¹¹ are important since they show that type 1 DM have a strong role in the development of periodontitis in early childhood. In contrast, previous studies showed that there were no significant differences in the values of periodontal parameters in children with type 1 DM, compared to the control group^{13, 14}. These findings can be explained by the differences in the susceptibility to periodontitis between different subpopulations with type 1 DM, such as race, gender, etc. One of the important reasons supporting these findings can be the fact that the authors of the previous studies measured CAL, but not the total periodontitis-affected teeth and sites. A significant correlation between the duration of the disease, its metabolic control and gingival inflammation presented by the relationship between bleeding and dental biofilm was found by analysing the relation of the clinical parameters of diabetes with the number of teeth affected by periodontal infection (defined as any loss of epithelial attachment level visible on minimum of two non-adjacent teeth)¹². It indicates once again that in young patients with type 1 DM the duration of the disease and metabolic control have an impact on the prevalence of gingival inflammation and progression toward periodontitis and that there is a higher risk of developing more severe forms of periodontitis^{11, 12, 17, 30}. Besides, the study of Foia et al.³¹ clearly showed that children and adolescents are susceptible to destructive types of periodontitis, especially when the external etiological factors (microbial flora) are associated with diabetes. These data can be interpreted by the lack of metabolic control which increases the risk of developing gingival inflammation and hinders the healing of the incurred damage.

Diagnostic biomarkers of periodontitis and type 1 diabetes mellitus

An early detection of the disease has an important role in the success of therapy. If the disease is diagnosed earlier, the chances for a successful treatment are increased, or, if impossible, a better control of the disease course is enabled. In most cases, the diagnosis is established only after the development of the first symptoms of the disease. Therefore, in order to increase the rate of early detection of diseases, researchers are focused on identifying biomarkers which could indicate the presence of the disease prior to the manifestation of clinical symptoms³².

One of the trends in the development of early diagnosis of periodontitis is the development of disease monitoring mechanisms. Basic and regular clinical and radiographic measurements are useful for the detection and the diagnosis

of the disease, but nowadays disease markers in saliva are increasingly used as diagnostic tests for periodontitis³³. Saliva is used primarily because it is an ultrafiltrate of plasma and a body fluid which can be collected easily and non-invasively making it suitable for investigating biochemical parameters such as free oxygen radicals, lipid peroxidation products, such as malondialdehyde (MDA) and cytokines. Even so, the examinations of the composition of saliva in children with Type 1 DM are scarce. Aren et al.¹⁸ were one of the few who examined the composition saliva and found that the saliva of children with Type 1 DM had a lower pH and buffering capacity, whereas the peroxidase activity and the glucose, magnesium and calcium levels were increased compared to healthy children. Besides this, a positive correlation was demonstrated between the peroxidase activity of gingival exudates and the severity of gingival inflammation, as well as the periodontal pocket depth. Additionally, MDA level in saliva and plasma^{34, 35} and cytokine level in the gingival crevicular fluid³⁶ and in the serum³⁷ were statistically significantly increased in patients with DM and gingivitis or periodontitis compared to healthy individuals, so more attention has recently been directed to the analysis of saliva in diabetic patients. Various studies have demonstrated that the biological activity of cytokines can directly influence the degree of periodontal destruction (epithelial attachment loss, destruction of collagen and alveolar bone resorption)^{38, 39}. The individual course of periodontitis indicates the importance of conducting complex researches of cytokines responsible for the beginning, progression and/or suppression of the immune response⁴⁰. However, only a few studies have investigated local periodontal inflammation at the biochemical and immunological level in patients with DM. The latest findings suggest that hyperglycaemia can lead to the increased production of inflammatory mediators, e.g. Engbretson et al.⁴¹ demonstrated that inadequate metabolic control was associated with an elevated level of interleukin-1 β (IL-1 β) in the gingival crevicular fluid. These data also indicate the mechanism which explains the relationship between poor metabolic control and periodontal destruction. Hypertriglyceridemia, which is accompanied by DM, leads to an increased production of pro-inflammatory mediators in monocytes, such as tumor necrosis factor- α (TNF- α) and IL-1 β , while neutrophils produce more IL-1 β accompanied by the disorders of chemotaxis and phagocytosis. The increased level of pro-inflammatory mediators, which can be used for diagnostic purposes, was found not only in serum, but also in the gingival crevicular fluid of hyperlipidemic patients with type 2 DM^{42, 43}.

It is assumed that patients with periodontitis can have increased levels of some circulating inflammatory markers. Periodontal monocytes, macrophages, fibroblasts and endothelial cells respond to the microorganisms, lipopolysaccharides and other antigens of the dental biofilm, and secrete numerous chemokines and inflammatory cytokines, primarily TNF- α , prostaglandin E2 (PGE2) and interleukins (IL-1 β and IL-6), in the systemic circulation. Advanced glycation end products (AGE), accumulated in monocytes due to hyperglycemia, and their binding to their dedicated receptors

(RAGE) increases the oxidative stress in cells and activates the transcription nuclear factor-kappa B (NF- κ B) which influences the phenotype of monocytes/macrophages and leads to the increased production of proinflammatory cytokines, such as IL-8 and TNF- α .⁴⁴ This increased production of proinflammatory cytokines is critical for the chronic inflammatory processes in the formation of atheromatous lesions in large blood vessels^{45, 46}. Through the oxidative stress, DM affects the inflammatory processes in the gingiva by increasing the accumulation of AGE-modified protein⁴⁷. The levels of IL-8, TNF- α and PGE2 in the gingival crevicular fluid are increased in patients with DM compared to healthy individuals due to the interaction between the AGE-modified protein and RAGE receptor in the periodontal tissues.

IL-8 is a proinflammatory cytokine that plays a significant role in the pathogenesis of periodontitis in patients with DM, especially in those with poor metabolic control. The study of Erbađci et al.⁴⁸ showed that the level of serum IL-8 was significantly higher in children and adolescents with type 1 DM compared to the systemically healthy children while maintaining a correlation between age, weight, lipid status, apolipoproteins and glycaemic control. In the same group of subjects, the concentration of IL-8 in saliva was also statistically much higher in children with type 1 DM⁴⁹. However, a statistically significant difference was not found when the level of IL-8 in the saliva of children with type 1 DM and concomitant periodontitis was compared to children with only type 1 DM. This was the first examination of salivary inflammatory mediators in children and adolescents with type 1 DM accompanied by periodontitis. Having in mind that the advanced periodontitis can cause an additional increase in the level of IL-8 in the saliva, the authors of this study determined the severity of periodontitis. The average PPD in children with type 1 DM and periodontitis was 2.05 mm, while the average value of CAL was 1.31 mm, demonstrating that periodontitis was in its initial phase. Considering that there was no correlation between the periodontal parameters and the level of IL-8 in saliva, the authors concluded that the increased level of salivary IL-8 was caused by the presence of metabolic changes related to DM and not by periodontitis. The source of the elevated IL-8 level could be hyperglycaemia which can induce the transcription of IL-8 gene in human endothelial cells⁵⁰. In addition, it was shown that hyperglycaemia and ketosis regulate the production of IL-8 in cultivated monocytes⁵¹.

Besides IL-8, according to the results of Karlsson et al.⁵², the level of interferon- γ (IFN- γ) in peripheral mononuclear cells in children and adolescents with type 1 DM with good and poor metabolic control was statistically much higher compared to the control group of healthy children and adolescents. According to the same authors' data, the elevated level of IFN- γ caused adaptation or improvement of the immune response to infection. Contrary to Karlsson et al.⁵², a statistically significant increase in the level of IFN- γ was not found in the serum⁴⁸ and saliva⁴⁹ of patients with type 1 DM and periodontitis, although the level of IFN- γ in children with type 1 DM was 17% higher compared to healthy subjects. Considering that saliva is an ultrafiltrate of

plasma, an increased serum level of IFN- γ was not reflected in the saliva, because it is a large molecule that probably could not pass easily through the capillary endothelium of the oral mucosa. Taking into account that IL-5 and IL-4 have some common characteristics in relation to the reduced infection sensitivity, it is important that Karlsson et al.⁵² found that patients with type 1 DM had a statistically significant increase in the relationship of both markers to the IFN- γ level in blood. Accordingly, the results of Karlsson et al.⁵² and Foss Freitas et al.⁵³ show that the favorable relationship between the increased levels of IFN- γ and IL-5 represents an adequate response of the immune system to an inflammatory process in the oral cavity (i.e. periodontitis). It should be stressed that another study showed that the large difference in the increase of the level of IL-5 compared to IFN- γ (4.8 times) in the saliva was statistically much higher, and that the level of IL-5 in the saliva of children with type 1 DM was increased by 81.8% compared to the results of the control group⁵⁴. The increasing tendency draws attention supported by the assumption that the determination of the IL-5 level may serve as one of the markers of the degree of inflammation.

The development of molecular biology in clarifying insulin resistance and dysfunction of β -cells has enabled the identification of the increased role of inflammatory mediators, especially cytokines and elements of the innate immune system in the pathogenesis of type 2 DM⁵⁵. The production of cytokines as a result of infection could potentially contribute to the insulin resistance in numerous ways. In contrast, children and adolescents with type 1 DM depended solely on the exogenous insulin, whose rhythmic intake effects glucose metabolism in an uneven way. This is exactly the reason why the general condition of children and adolescents was disrupted in the following years, and therefore at greater risk of developing a severe form of periodontitis. Thus, similar to adults, the parallelism can be expected between the severe form of periodontitis and a significant increase in the levels of cytokines, which would hamper their dental care.

Conclusion

Type 1 diabetes mellitus is a significant etiopathogenic factor responsible for the development of diabetic periodontitis. This is confirmed by a statistically significant increase in the incidence and proinflammatory condition of the entire organism. Hyperglycaemia damages periodontal tissues through several mechanisms, primarily due to the damages of the mechanism of immune response, non-enzymatic glycosylation and increased oxidative stress.

In terms of a very high incidence of both diseases and their potentially serious repercussions, other medical specialists should have an important role in encouraging patients to visit their dentists regularly in order to control the etiological factors, especially the dental biofilm. Dentists should also bear in mind that the deterioration of glycolic metabolism and diabetes may deteriorate the condition of periodontitis. Contemporary literature on the treatment of children and

adolescents suffering from the aforementioned diseases emphasises the need for the regular application of the following analysis and procedures: glycemic values, HbA1C and the most significant biochemical parameters of DM, because hyperglycaemia has a negative impact on the anti-inflammatory response and increases the oxidative stress of microvascular disorder in periodontal tissues. It is essential to have a protocol for the treatment of periodontitis, which involves the local periodontal mechanical treatment as well as local and systemic medication treatment. The elimination of periodontal pathogens from the periodontal, pockets reduces the intensity of local inflammation, thus improving the overall condition of the body, because of the positive effect on the overall condition of glucose regulation.

Besides that periodontitis has already been defined as the sixth complication of diabetes mellitus, the results of numerous studies imply that periodontitis is an inflammation with the pos-

sible systemic response and subsequent disorder of glucose regulation.

In addition to the regular procedures in monitoring the condition and prognosis of diabetes and periodontitis, the analyses of saliva and gingival crevicular fluid are also recommended as non-invasive and relatively reliable sources of information on the aforementioned diseases. Therefore, the cooperation between pediatric endocrinologists and dentists is required in order to preserve and improve the general health of children and adolescents.

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**Findings of clinical studies which investigated the correlaton beetwen type 1 diabetes mellitus (DM)
and periodontal disease**

Author/ year	Study popu- lation	Duration of diabetes mellitus Type 1 (years)	Glycated haemoglobin level – HbA1c (%)	Gingival parameters	Periodontal parameters	Main findings
Rylander et al. 1987. ⁵⁶	46 patients with DM1 mean age 22.1 ± 4.7 41 healthy individuals mean age 22.3 ± 2.1	10–14 years – 24 children 15–19 years – 20 children > 20 years – 2 children	< 7.0 – 2 children 7.0–8.9 – 13 children 9.0–11.9 – 17 children 12.0–13.9 – 12 children > 14.0 – 2 children	PI GI	PPD (mm) only probing depths of > 3 mm CAL (mm) measured at 4 sites around each tooth GR (mm)	Higher frequency with clinical attachment loss on buccal sites, and GR in diabetic group than in the control group. The presence of dental biofilm on these tooth surfaces was equally low in the 2 groups; in interproximal regions very low frequency of periodontal tissue breakdown
Rosenthal et al. 1988. ⁵⁷	52 patients with DM1 mean 14.5 years	NR	Patients with DM1 without periodontitis HbA1c – 12.56% DM1 patients with periodontitis HbA1c – 9.17%	PI GI SBI	PPD (mm) measured at 4 sites around each tooth	GI and SBI were significantly higher in the periodontitis group. PI was not significantly different between the groups. Diabetics with periodontitis had a significantly lower glycosylated hemoglobin than diabetics without periodontitis
Sandholm et al. 1989. ⁵⁸	85 patients with DM1 mean 15.1 ± 1.5 SV years 85 healthy adolescents mean 15.1 ± 1.6 years	mean 5.2 ± 3.5 years	mean 10.9 ± 2.2 (SD)	PI GI RC	CPITN (reg- istrated using 16, 21, 26, 36, 41 and 46 as index teeth) PPD (mm) measured at 4 sites around each tooth	Finnish adolescents with DM1 had more gingivitis than their age- and sex-matched healthy controls. There were no differences in periodontal destruction as measured in number of pockets > 4 mm. All gingivitis does not lead to periodontitis, but periodontitis preceded by gingivitis
Pinson et al. 1995. ¹⁴	26 patients with DM1 mean 13.50 ± 3.36 years included one set of identical twins 24 control subjects mean 13.54 ± 3.08 years	mean 6.58 ± 3.66 years, with 24 of the patients having had DM1 for at least 5 years	3.4–6.1 – 6 children 6.2–9.0 – 9 children > 9.0 – 11 children	PI GI gingival bleeding on probing	PPD (mm) measured at 4 sites of each tooth CAL (mm) measured at 4 sites around each tooth GR (mm)	Significant association of age with pocket probing depth, clinical attachment levels, and bleeding in the diabetic group. Duration of diabetics and metabolic control level were not related to periodontal parameters. DM1 had a significant association with severity of periodontitis when tooth sites in patients groups were statistically compared
Kar- jalainen et Knuutila 1996. ⁵⁹	12 patients with DM1 mean 10.6 ± 2.4 years 80 healthy subjects mean 14.5 ± 1.6 years	NR	on the 3rd day in hospi- tal 14.9 ± 3.8% on the 12rd day in hos- pital 13.1 ± 2.9% on the 1st outpatient visit at the hospital 1 month later 8.4 ± 1.5%	PI % of visi- ble plaque gingival bleeding on probing % of bleeding surfaces	NR	Hyperglycaemia and poor metabolic control of diabetes increased gingival bleeding. Not all gingivitis proceeds into a destructive periodontal disease. Lower resistance toward dental plaque in poorly-controlled patients indicates that biological alterations could take place during glucose balance deterioration
Firatli 1997. ¹⁶	77 patients with DM1 mean age 12.47 years 77 healthy volunteers mean age 12.59 years	mean 48.34 ± 23.69 months	children with DM1 9.34 ± 3.99% control group 5.96 ± 1.02%	PI GI gingival bleeding on probing	PPD (mm) measured at 4 sites of each tooth CAL (mm) measured at 4 sites around each tooth	A positive correlation between the duration of DM1 and CAL. Relationship between the duration of DM1 and severity of periodontal alterations
Aren et al. 2003. ¹⁸	Group 1: 16 newly di- agnosed chil- dren; mean age 12.8 ± 5.8 Group 2: 16 children with diabetes of long dura- tion; mean age 12.7 ± 3.8 Group 3: 16 healthy	Children in Group 1 with newly diag- nosed DM1 and Group 2 with diabetes of long duration;	Group 1 8.01 ± 1.79 % Group 2 8.43 ± 1.36 % Group 3 5.05 ± 0.36 %	PI GI gingival bleeding on probing	PPD (mm)	Glycaemic status of the diabetic subjects affects the periodontal probing depths, salivary pH, buffering capacity, and peroxidase activity.

	subjects; mean age 12.4 ± 1.9					
Lalla et al. 2006. ¹¹	182 patients with DM1 mean 11.9 ± 3.3 years 160 healthy children mean 10.9 ± 2.6 years	mean 4.5 ± 8.0 years Age of diagnosis DM1 mean 7.8 ± 4.0 years	< 7.5% – 55 children 7.5–9.5% – 80 children > 9.5% – 36 children	PI % of sites PI GI % of bleeding sites GI score of 2 or 3 denotes a bleeding site	PPD (mm) measured at 4 sites of each tooth CAL (mm) measured at 4 sites around each tooth Number of affected teeth (at least one site with attachment loss > 2 mm on at least two teeth)	Periodontal destruction was increased in children and adolescents with DM1. Diabetes started earlier in life than formerly recognized. Duration of DM1, and especially mean A1c, were not significantly correlated with the number of affected teeth.
Lalla et al. 2007. ¹⁷	350 patients with DM1 mean 11.33 ± 3.41 years	mean 3.96 ± 3.39 years Age of diagnosis DM1 mean 7.54 ± 4.0 years	< 7.5% – 97 children 7.5–9.5% – 170 children > 9.5% – 73 children	PI % of sites PI GI % of bleeding sites GI GI score of 2 or 3 denotes a bleeding site	PPD (mm) measured at 4 sites of each tooth CAL (mm) measured at 4 sites around each tooth Number of affected teeth (at least one site with attachment loss > 2 mm on at least two teeth)	Increased periodontal destruction in children and adolescents with DM1 was connected with increased metabolic control. If gingival bleeding and attachment loss measurements were both used, the present study revealed that hemoglobin A1c significantly correlated with periodontitis
Daković and Pavlović 2008. ¹²	187 patients with DM1 mean 12.4 ± 4.2 years 178 healthy children mean 11.4 ± 4.3 years	mean 4.9 ± 3.5 years Age of diagnosis DM1 mean 7.9 ± 4.2 years	< 7.5% – 20 children 7.5–9.5% – 95 children > 9.5% – 65 children	PI % of sites PI GI % of bleeding sites GI GBI bleeding/plaque ratio	PPD (mm) measured at 4 sites of each tooth CAL (mm) measured at 4 sites around each tooth Number (%) of patients with periodontitis and any level of CAL, and CAL > 1,5 mm	Periodontal disease was more prevalent in children with DM1 and was in function of metabolic control and disease duration. The gingival inflammation in the evolution of periodontal destruction was more important in children with DM1 than in subjects without the disease
Foia et al. 2011. ³¹	42 patients with DM1 and periodontitis 42 non-diabetic subjects with periodontitis The subjects were divided into subgroups, according to the age and metabolic control of DM1	NR	< 7% – 22 children > 7% – 20 children	PI GBI	CAL (mm) measured at 4 sites around each tooth	All studies on clinical parameters referring to periodontal status in diabetic children were much higher than those in systemically healthy group. Children were susceptible to periodontal destruction, especially when the etiologic external factors were associated with host related systemic impairment, such as insulin dependent diabetes. Systemic diseased metabolic balance was significantly connected with Gram-negative species-mediated cytokine translocation from the periodontal space into the circulation.

PI – plaque index; PPD – pocket probing depth; GR – gingival recession; GI – gingival index; CAL – clinical attachment level; NR – not reported; SBI – sulcus bleeding index; RCI – retentive calculus index; CPITN – community periodontal index of treatment needs; GBI – gingival bleeding index.