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Factors contributing to the development of diseases of the oral mucosa and gums in children with type 1 diabetes

Czynniki sprzyjające rozwojowi chorób błony śluzowej jamy ustnej oraz dziąseł u dzieci z cukrzycą typu 1

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Key words

diabetes mellitus type 1, gingivitis, oral candidiasis

Słowa kluczowe

cukrzyca, zapalenie dziąseł, kandydoza jamy ustnej

Summary

Introduction. Oral mucosal infections occur more often in patients with diabetes mellitus type 1 than in healthy population.

Aim. The aim of the study was to analyze factors contributing to diseases of the oral mucosa and gums in diabetic children.

Material and methods. Study group: 41 children with diabetes type 1 (18 boys and 23 girls of 5.33-17.83 years, mean age 12.92 ± 3.02); control group included 39 children (19 boys and 20 girls aged 4-17.75 years, mean age 11 ± 3.82). Dental examinations were performed to assess oral hygiene status (OHI-S), the state of oral mucous membrane, gums (GI) and teeth (DMFT/dmft). Material was collected for bacteriological and mycological examination and for evaluation of the physical and chemical properties of saliva. Laboratory rated exponents for control of diabetes were performed.

Results. No differences were found in the percentage of *Candida* spp. between study group and control. Gingivitis was observed with comparable frequency in both groups. The percentage of children with no signs of gingivitis was significantly higher in the control group (20 vs. 33%), while mild gingivitis was more often observed in children with diabetes (68 vs. 46%). *Candida* spp. infections were more frequent in children with elevated HbA1c. Cheilitis and atrophic glossitis were more often reported for diabetic children. HbA1c level positively correlated with atrophic glossitis, gingivitis, cheilitis and the presence of *Lactobacillus acidophilus*.

Conclusions. Metabolic disorders characteristic for diabetes favor the emergence of oral mucosa and gum diseases. No differences in the incidence rate for fungal gingivitis were observed between diabetic children and controls which may be attributed to more frequent pediatric and dental inspections associated with special care and monitoring of diabetic children.

Streszczenie

Wstęp. Uważa się, że u osób z cukrzycą 1 typu częściej niż u zdrowych występują infekcje błony śluzowej jamy ustnej.

Cel pracy. Celem pracy była analiza czynników sprzyjających chorobom błony śluzowej jamy ustnej i dziąseł u dzieci z cukrzycą typu 1.

Materiał i metody. Grupa badana liczyła 41 dzieci z cukrzycą: 18 chłopców i 23 dziewczynki w wieku 5,33-17,83 roku (średni wiek 12,92 ± 3,02), grupa kontrolna – 39 dzieci: 19 chłopców i 20 dziewczynek w wieku 4-17,75 roku (średni wiek 11 ± 3,82). U wszystkich przeprowadzono badanie stomatologiczne oceniające stan higieny jamy ustnej (ang. *Oral Hygiene Index-Simplified* – OHI-S), błony śluzowej, dziąseł (wskaźnik dziąsłowy, ang. *Gingival Index* – GI) i zębów (wskaźnik PUW/puw), pobrano materiał do badania bakteriologicznego, mikologicznego oraz oceny parametrów fizykochemicznych śliny. Oceniono wybrane wykładniki wyrównania cukrzycy.

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Wyniki. Nie stwierdzono różnic w odsetku obecności *Candida* spp. między grupami dzieci z cukrzycą i kontrolną, zapalenie dziąseł występowało z porównywalną częstością, odsetek dzieci bez cech stanu zapalnego dziąseł był istotnie wyższy w grupie kontrolnej (20 vs. 33%), łagodne zapalenie dziąseł częściej występowało u dzieci z cukrzycą (68 vs. 46%). Występowanie zakażeń Candida spp. było częstsze u dzieci z podwyższonym poziomem HbA1c. U dzieci z cukrzycą częściej występowały zapalenia kącików ust oraz zanikowe zapalenie języka, poziom HbA1c pozytywnie korelował z zanikowym zapaleniem języka, zapaleniem dziąseł, zapaleniem kącików ust, obecnością *Lactobacillus acidophillus*.

Wnioski. Zaburzenia wyrównania metabolicznego w cukrzycy sprzyjają pojawianiu się chorób błony śluzowej jamy ustnej i dziąseł. Brak różnicy w częstości występowania grzybów *Candida* spp. oraz zapaleń dziąseł między grupami badaną i kontrolną tłumaczyć można częstszymi kontrolami pediatrycznymi wynikającymi z prowadzenia cukrzycy oraz częstszą kontrolą stomatologiczną tych dzieci.

INTRODUCTION

Diabetes mellitus type 1 is a term used to describe a severe metabolic disorder induced by insulin-deficiency. The disease results from the destruction of insulin-producing pancreatic beta cells in Langerhans islets by a beta-cell specific autoimmune process which involves T lymphocytes and macrophages. In diabetes type 1 the destruction of pancreatic beta-cells (*insulitis*) as result of inflammatory-cell /lymphocyte infiltration of insulin-producing pancreatic inslets constitutes the initiary phase of autoagression. The process of beta-cell destruction involves subpopulations of T lymphocytes (mostly Th1, Th2), cytotoxic lymphocytes CD8+, NK cells, macrophages/monocytes and mediators of inflammation secreted by immunocompetent cells (cytokines, free radicals/cytokine-induced free radicals) (1-4).

Diabetes-induced complications range from acute ketoacidosis and coma to long-term complications in different organs (retinopathy, nephropathy, cardiomyopathy, neuropathy) with diabetic angiopathy as the underlying factor.

Adequate/Good glycaemic control is the main target in the management of diabetes.

Inadequate/Poor control of diabetes not only results in long-term complications but also enhances susceptibility to bacterial and fungal infections one of which is yeast colonization of the oral cavity. Such colonization is not univocal to infection; an effective immune system of healthy people protects them against yeast-like fungi invasion and no pathological lesions are observed. Colonization progresses to infection only when the natural host-fungi equilibrium is disturbed. *Candida albicans* is the most frequent cause of oral infections. Colonization and tissue invasion by this bacteria species is facilitated by its morphological diversity, ability to adhere to host epithelial and endothelial cells, extracellular enzyme production and immunomodulative effect of *Candida* spp. antigens (5).

An important role in the antifungal host defense system is attributed to the oral milieu (e.g. mucosal integrity, antifungal effect of saliva, fungi-microflora interaction), defense mechanisms particularly related to phagocytic cells/phagocytes (mostly neutrophils) as well as specific cellular response.

Yeast-like oral infection promoting factors are:

I. Changes in secretion flow and biochemical parameters/composition of saliva i.e. higher glucose level, lower salivary pH, elevated salivary amylase, and oral mucosal injury (thickened capillary endothelium impairs oxygen flow and metabolic waste removal). Pathogenesis of salivary secretion in diabetic patients is not yet fully recognized. Clinical symptoms presented by diabetic patients include swollen salivary glands, especially parotid glands. Labial salivary glands of diabetic children reveal lymphocyte infiltrations similar to pancreatic infiltrations; this may be suggestive of similar or even identical autoimmune pathology (6). Disorders in salivary secretion may also be attributed to: angiopathy, neuropathy, smaller number of receptors on the surface of gland cells. Lower salivary secretion may also be attributed to poliuria, water balance disorders as well as medication administered for treatment of diabetic complications (7-10).

In diabetic children changes in salivary parameters/composition have also been observed. Literature reports on this subject vary mostly likely due to different study methods. Some authors report a marked decrease in total protein level, increase of salivary α-amylase and lactate dehydrogenase especially in children with poor glycemic control (6). Low saliva volume impairs oral self-purification and therefore favours dental plaque retention (11). In addition, higher glucose concentration in saliva and gum fluid may alter the living-conditions of bacteria and modify the microbial composition of the oral cavity. This may induce the development of oral infections, dental caries and periodontal diseases (12). The crucial factor here is high salivary glucose level observed also in patients with adequate diabetes control. Infections may also be attributed to plaque-pathogens which promote fungal infections. It is believed that the oral microflora/bacterial flora of diabetics is specifically changed and by producing leukotoxins may disturb neutrophil activity and bring on the inflammatory process (13).

II. The immunological response may also be disturbed by nonspecific factors such as:

1. Impairment of such neutrophil activity as: phagocytosis, intra-cellular pathogen elimination, adhesion

and chemotaxis (14-16). Disturbance of the activity of these cells is closely related to the level of metabolic disorders observed in diabetic patients with poor diabetic control, elevated HbA1c levels and chronic/long-term diabetes (17).

In a hyperglicemic environment nonenzymatic glycosylation occurs on many proteins. The advanced glycation end products (AGE) play an important role in cell migration, phagocytic activity of macrophages/monocytes and finally lead to abundance of pathogenic bacterial and fungal flora in the oral cavity. Infection intensifies the oxidative stress and insulin resistance and so disturbs the regulatory secretion of proinflammatory TNF-α and IL-1. Oral infections may be induced by hyperglicemia, insulin resistance, accumulation of AGE proteins which cause degradation, destruction and proliferation of the connective tissue proteins. As result of non-enzymatic protein glycation there occurs disturbance in collagen synthesis, maturation and homeostasis followed by lower collagen resistance to change and impairment of blood vessel integrity (18-20).

In diabetic patients the level of immunoglobulin glycation has also been reported as higher for IgM than for IgG as well as impaired agglutination of IgM. It is believed that the high level of glycolized IgM reported in the early phase of acute infection negatively affect the immunological response (21, 22).

2. Cellular immunodeficiency

It has been demonstrated that in response to *Candida* spp. antigens there occurs a type Th1 immunological response characterized by high/increased interleukin 2 (IL-2) and IFN-gamma (IFN-γ) production while the levels of interleukin 4 (IL-4) and interleukin 10 (IL-10) production are low or null. Lower levels of T lymphocytes with regulatory CD+4 phenotype have also been demonstrated (23, 24).

Inadequate diabetic control leads to predominance of catabolic over anabolic processes with negative impact on inflammatory processes (23). Gingivitis and higher risk of parodontosis have been more frequently observed in diabetic children and adolescents than in healthy persons. These are fostered by: dental plaque, vascular changes in the marginal gingival, collagen metabolism disturbances and increased collagenase induced by hyperglycemia and wound healing impairment (25).

Up-to-date studies report that diabetes not only increases the risk of oral mucosa diseases but also impairs clinical treatment. Nowadays, the negative impact of oral diseases especially paradontium on management of diabetic patients is being strongly emphasized. It has been demonstrated that any inflammatory condition impairs diabetic control of a diabetic patient. Infections markedly increase insulin intake and therefore impede reaching normal range blood glucose levels (26).

AIM

The aim of the study was to assess the oral status of children with type 1 diabetes and analysis of factors that foster oral mucosa and gum diseases.

MATERIAL AND METHODS

The study included 41 children with type 1 diabetes (18 boys and 23 girls aged 5.33 to 17.83 years; mean age 12.92 $\pm$ 3.02) all patients of the Endocrinological Department and the out-patient clinic. The group was diversified for disease duration, age and control of diabetes.

Dental examination was performed during control visits at the outpatient clinic or during hospitalization. Management was based on insulin analogous (personal insulin pump) or intensive injection therapy. The control group comprised 39 healthy children (no diabetes or any other chronic disease). It consisted of 19 boys and 20 girls aged 4.17-17.75 years (mean age 11 $\pm$ 3.82).

All children were subjected to dental examination which included assessment of oral mucosa (frequency rate, site and scope of such specific lesions as cheilitis, atrophic glossitis, linea alba, lingual/tongue coating, mappy tongue), dental status according to DMFT index as well as micro hardness of mineralized tooth tissues. Oral hygiene status was assessed using the simplified Greene and Vermillion Oral Hygiene Index (OHI-S) (28) with mean OHI-S index values as baseline. Index values of 0.0-1.0, > 1.0-2.0 and > 2.0-3 indicated good, satisfactory and poor oral hygiene status respectively (28).

The Silness-Löe Gingival Index (GI) was used to determine the degree of bleeding (30). The index was calculated from the mean number of individual bleeding sites (teeth). Mild gingivitis was recognized at GI: 0.1-1.0, moderate at > 1.0-2.0 and severe at GI > 2.0.

Laboratory diagnosis of *Candida* spp. and enzymatic test reaction was based on positive cultures from urine and direct oral mucosal smears with the use of API20C AUX and API tests.

Physicochemical parameters of saliva were tested in the morning, 2 hours after the last meal with commercial Saliva Buffer (GC) test for pH, buffer effect, consistency and viscosity of resting saliva as well as secretion rate of stimulated saliva. Normal pH range for resting saliva was estimated at pH – 6.8-7.8; pH values of 6.0-6.6 – were classified as moderately acidic, while 5.0-5.8 values were evaluated as acidic.

The titer of *Streptococcus mutans* and *Lactobacillus acidophilus* was determined from saliva cultures on commercial CRT Bacteria (Ivoclar Vivadent culture media). High titer was identified at > 10^5 CFU.

In the study group of diabetic children we assessed the laboratory parameters for diabetic control: level of glycosylated hemoglobin (hemoglobin A1c), blood glucose levels, glycosuria at collection of material for dental examination, triglycerides and total cholesterol (tab. 1).

Statistical analysis of test results was performed with Statitica 7.1. using descriptive statistics, correlation matrix and comparative t tests. Statistical significance was determined at $p < 0.05$.

RESULTS

Statistical analysis showed no differences in oral hygiene status between children with diabetes and controls. In both groups the mean OHI-S index fell within

Table 1. Selected parameters for assessment of diabetic control in patients with type 1 diabetes.

	Disease duration		
	0-1 years	> 1-5 years	> 5 years
No. of children (41)	15	12	14
HbA1c (%)	9.64	7.02	8.75
Cholesterol (mg/dl)	166	182	173
Triglycerides (mg/dl)	80	87	84
BMI (kg/m^2)	18.7	20.3	20.5
Insulin dose (u/kg b.m./24 h)	0.48	0.94	0.84

the > 1.0-2.0 – range and was considered satisfactory. The index however only slightly exceeded 1.0 (mean index value for children with diabetes 1.053, min. – 0.33, max. – 2.0; the mean index for controls was 1.021: min. – 0.08, max. – 2.5). The mean index values for the diabetic group were: good oral hygiene status for 20 children (49%) and satisfactory for 21 (51%). The mean index values for the control group were: good oral hygiene status for 22 children (56.4%), satisfactory for 15 (38.4%) and unsatisfactory for 2 (5.2%) (tab. 2).

Table 2. Oral hygiene status assessed with OHI-S index – comparison between study group and control group.

OHI index	Good 0.0-1.0	Satisfactory > 1.0-2.0	Unsatisfactory > 2.0-3.0
Children with diabetes (1.053)	20 (48.8%)	21 (51.2%)	0
Control group (1.021)	22 (56.4%)	15 (38.4%)	2 (5.2%)

The mean index value for the whole groups did not reflect the true state of things.

The prevalence/frequency of oral mucosa lesions was comparable in both groups. In the study group mucosa lesions were observed in 58.5% of children and in 12.8% of the control group. The frequency of various types of lesions is presented in table 3.

Table 3. Frequency of various mucosa lesions in both groups.

	Children with diabetes (%)	Control group (%)	Statistical significance of the difference
Oral mucosa lesions	58.5	12.8	< 0.000
Cheilitis	7.3	0.0	0.085
Atrophic glossitis	14.6	0.0	0.013
Linea alba	24.4	0.0	0.001
Lingua/tongue coating	39.0	7.7	0.001
Mapping tongue	0.0	5.1	0.142

We then used the GI index to analyze the state of gums (gingivitis). In the control group the number of children without gingivitis was significantly higher than in the study group; 33 vs. 20%. The analysis of degree of gingivitis demonstrated higher prevalence of mild gingivitis (GI: 0.1-1.0) in diabetic children (28 patients – 68%) as compared to 18 children (46%) with mild gingivitis in the control group (fig. 1).

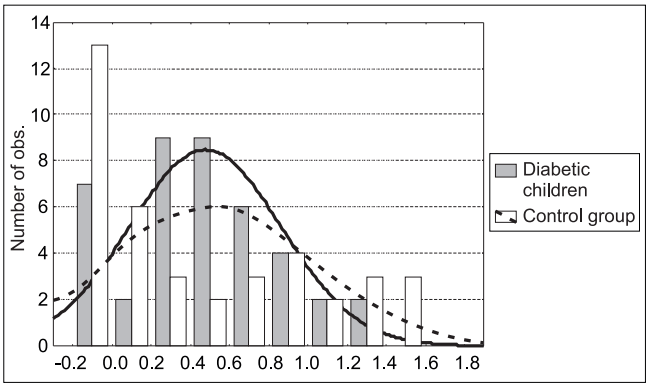

Fig. 1. Distribution of GI – values for oral mucosa lesions in both groups.

In diabetic children oral mucosal lesions positively correlated with the HbA1c level. Positive correlation was found between atrophic glossitis, gingivitis, cheilitis, Lactobacillus acidophilus (LA) and HbA1c level. Data was compared in table 4 and figure 2. No significant relationship was found between oral mucosa lesions and glycemia levels at examination.

Table 4. Correlation between selected parameters of oral hygiene and HbA1c. Correlation indexes at P < 0.05.

	Mean GI	LA > 10^5	Cheilitis	Atrophic glossitis	*Candida albicans*
HbA1c	0.394	0.461	0.349	0.461	0.422

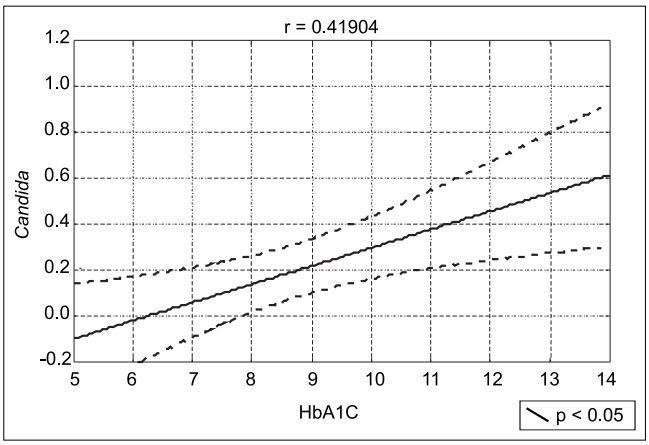

Fig. 2. Correlation between *Candida* spp. infection and HbA1c level.

The pH of resting saliva was significantly lower for diabetic children than for controls. The mean pH value for resting saliva in diabetic children was 6.77 and 7.23 for controls. The difference was statistically significant (P < 0.01) (tab. 5).

No statistically significant differences in *Candida* spp. infection were found between groups. It has been demonstrated that in diabetic children *Candida* spp.

Table 5. Distribution of salivary pH values in both groups.

	pH 5.0-5.8	pH 6.0-6.6	pH 6.8-7.8
Children with diabetes (n = 41)	1 (2.4%)	19 (46.4%)	21 (51.2%)
Control group (n = 39)	2 (5.1%)	5 (12.8%)	32 (82.1%)

correlated positively with HbA1c level. In children with higher HbA1c levels *Candida* spp. infection was more frequently recognized (fig. 2).

DISCUSSION

As in other immunodeficiency disorders (long-term sterydotherapy, cytotoxic therapy, primary and secondary immunodeficiencies) also in diabetes type 1 the prevalence of oral mucosa diseases including yeast infections is higher than in the general population (30-37). Most studies confirm a higher frequency of oral candidiasis (*Candida* spp.) in patients with type 1 diabetes (38), there are however reports which do not confirm such relationship regardless of the type of diabetes (39).

In our study the percentage of *Candida* spp. cases did not differ between study group and the controls, we did however demonstrate a positive correlation between *Candida* spp. and HbA1c in diabetic children although the differences were not statistically significant. The highest HbA1c percentage was reported for children with newly recognized diabetes and diabetes of more than 5 year duration. This may prove that higher percentage of candidiasis may be attributed to factors other than duration of metabolic disorders before diagnosis, diabetes duration and oral hygiene status. Not only oral candidiasis has been reported as higher in both diabetes type 1 and 2 under poor diabetes control but hydrolytic enzyme production as well (40, 41). Possibly, if we had tested our study group with equally accurate methods we might have collected more information on the oral candidiasis in diabetic patients both before the onset of symptoms as well as for poor control of diabetes.

Both in the study group and controls we assessed the oral hygiene status using the Oral Higiene Index-Simplified (OHI-S). Statistical analysis presented no differences between the groups which may prove that special attention is paid to oral hygiene of diabetic children and dental control is more frequent.

The most significant problem for our diabetic patients was gingivitis measured with the GI index. In the study group we observed a higher frequency of mucosa lesions including mild gingivitis which positively correlated with HbA1c level. Moreover, we demonstrated positive correlation between HbA1c levels and atrophic glossitis, gingivitis, cheilitis, and the presence of *Lactobacillus acidophilus* (LA). Our results are consistent with the data of other authors who demonstrate higher prevalence of oral mucosa lesions in relation to poor diabetes control (42, 43). In an evaluation study of oral mucosa status of 300 children aged 6-18 years with type 1 diabetes Lalla et al. (44) also demonstrated the relationship between periodontal lesions and metabolic control assessed with HbA1c level. Another study of Lalla et al. (45) which included 182 diabetic children (aged 6-18 years) and 160 healthy controls revealed higher plaque accumulation and degree of gingivitis in diabetic children than in controls. In diabetic children destructive periodontal lesions may be observed very early and progress with age.

Taylor et al. (46) demonstrated that formation and accumulation of advanced glycation endproducts (AGEs) is implicated in the progression of oral pro-inflammatory processes in diabetic patients. The study showed that in patients as well as in animal models IL-1β, TNF-α, IL-6, OPG and RANKL cytokines may induce parodontitis in diabetic patients which is suggestive that the AGE-RAGE pathway plays a crucial role in cell destruction and impaired healing of diabetes-modified parodontitis/modified by diabetes. Not fully acknowledged is the role of locally active pro-parodontitis factors which in turn affect the course of diabetic management. Our study did not include the assessment of pro-inflammatory cytokine levels but in newly recognized diabetes they seem to play an important part in development of parodontosis.

Assessment of oral hygiene status in our study demonstrated that *Lactobacillus acidophilus* colonization occurs more frequently in diabetic children than in controls. *Lactobacillus acidophilus* is a Gram-positive bacteria, that enhances the onset of gingivitis, caries and/or development of other cariogenic bacteria in a hyperglecemic environment. These observations require further studies.

In the presented study we found the pH of resting saliva to be significantly lower in diabetic children which confirmed the results of Lopez et al. and Mata et al. (47, 48). Lower salivary pH is however a subject open to dispute (49, 50), as is the increased risk of caries (51, 52). There are contradictory reports regarding different salivary composition and secretion flow in diabetic patients (47, 51, 53, 54). Siudikiene et al. (55) demonstrated lower secretion of both stimulated and unstimulated saliva in patients with diabetes. Lopez et al. reported lower secretion rate for unstimulated saliva only (47). However, Belazi et al. (53) and Swanljung et al. (51) report no differences in salivary secretion between diabetic patients and health people.

CONCLUSIONS

1. In diabetic children hyperglicemia favours/enhances oral mucosa diseases and fungal *Candida* spp. infections.
2. Hyperglicemia favours colonization with *Lactobacillus acidophilus*, which promotes development of cariogenic bacteria.
3. In diabetic children pH of saliva is low due to hyperglicemia.
4. Lack of difference in the oral hygiene status between diabetic children and controls may be attributed to better parental care and lower consumption of monosaccarides.

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