

REVIEW

Oral manifestations of diabetes mellitus and influences of periodontological treatment on diabetes mellitus

Straka M

Department of Stomatology, Slovak Medical University, Bratislava, Slovakia. mudrstraka@r3.roburnet.sk

Abstract: The aim of this review was to describe and determine the oral manifestation of DM and influences of periodontological treatment on DM.

Diabetes mellitus (DM) is one of the most serious diseases of metabolism. Long-term consequences of hyperglycemia are very heterogeneous, and affect practically all tissues and organs of organism. Classical signs and symptoms of DM are polyphagia, polyuria, polydipsia, physical weakness, and decreased immunity against infections. Untreated and fully developed DM results in numerous complications, of which the most serious include nephropathies, retinopathies, myopathies, neuropathies, cardiovascular diseases, bad wound healing and disorders of microvasculature and macrovasculature. Oral manifestations of DM are of different types and they affect various tissues of this region.

Summarizing and comparing the literature data were used to obtain these goals.

From the etiopathogenetic viewpoint, we can state that the so far best-investigated oral complication is that of diabetic periodontitis and its consequences, including early teeth loss. Uncontrolled hyperglycemia deteriorates the periodontal status to the extent of developing into a clinical picture of diabetic periodontitis. On the other hand, it is to be noted that not all researchers have confirmed that the treatment of periodontitis brings about a statistically important improvement in diabetic markers, mainly HbA1c. It is necessary to continue in these studies (Ref. 34). Full Text in free PDF www.bmj.sk.

Key words: diabetes mellitus, periodontitis, hyperglycemia, AGEs, HbA1c.

The present classification of diabetes mellitus distinguishes types I and II of DM. Type I DM, previously referred to as insulin-dependent (IDDM), is a juvenile-onset diabetes mellitus afflicting 10 to 15 per cent of all patients with DM. It is caused by immunologically controlled autoimmune destruction of beta cells of the pancreas. Type I DM develops in childhood or in adolescent age, and is characterized with an absolute lack of insulin (1, 2).

A more frequent DM is the Type II, currently referred to as adult-onset diabetes and previously as non-insulin dependent diabetes mellitus (NIDDM). Its early state manifests as insulin resistance with inappropriate glucose tolerance. With increasing insulin resistance, there is also an increase in insulin production in the pancreas. As long as the production of beta cells of pancreas drops under 50 per cent, a pre-diabetic state arises, characterized with postprandial hyperglycemia, possibly remaining undiscovered during classical examinations. The latter state continuously advances into fully developed diabetes with various complications including those afflicting the oral tissues (1, 3).

The diagnostic screening of DM has been currently improved and simplified. Some studies indicate that in patients with gingi-

vit, periodontitis, and sufficiently bleeding oral tissues, blood from gingival sulcus or sac can be used (4). DM in oral region incurs diseases, also called oral complications of DM as listed below:

- Gingivitis and periodontitis
- Periradicular osteolytic inflammatory lesions and their various forms (acute and chronic periapical osteolytic lesions, odontogenous abscesses, granulomas etc.).
- Loss of teeth
- Xerostomia and changes of saliva composition
- Lesions of oral mucosa and tongue

Gingivitis and periodontitis

The most serious stomatological complication arising from diabetic disease is periodontitis (previously also referred to as parodontosis) that is always accompanied with developed gingivitis. Several studies state that DM of type II is a serious etiopathogenic factor of severe types of periodontitis. It increases the risk factor of developing periodontitis three-fold. These conclusions are confirmed also with other studies, in which it is quoted that insufficiently controlled glycemia increases the risk of periodontitis development by 2.9 times (5).

The clinical course of diabetic periodontitis is considerably heterogeneous. In young people (type I), the destruction of periodontal tissues starts relatively early, but it is more evidently

Department of Stomatology, Slovak Medical University, Bratislava, Slovakia

Address for correspondence: M. Straka, MD, PhD, Dept of Stomatology, Slovak Medical University, Krizna 44, SK-821 09 Bratislava, Slovakia.

Phone: +421.2.55424945

expressed in pre-pubertal and pubertal periods, depending on the duration of disease and presence of gingivitis and glycemic control (6). In patients suffering from DM of type II, pathological changes in periodontium can develop several years before the diagnosis of DM is established.

These pre-diabetic complications are in close relationship with the prevalence of hyperglycemic curves bound to food. Such postprandial hyperglycemias in pre-diabetic state of the disease stimulate the development of numerous diabetic complications, but they cannot be diagnosed by fasting glucose test (7).

Etiopathogenesis of diabetic periodontitis

Diabetes mellitus is a serious risk factor of destructive periodontitis. Its development and course can run through various mechanisms as follows:

Disorders of defensive and immune functions

Functional alteration of polymorphonuclear leucocytes is one of the basic immunological factors enabling the gram-negative bacterial infection to start a chronic process with its proteolytic and osteolytic enzymes. Several studies make us aware of the fact that changed functions of PMN leucocytes can be caused by disorders of chemotactic, adherent and phagocytic abilities of these cells. A decreased chemotaxis and transformation of PMN was detected in an animal experiment (7), and in patients with DM (1, 8). However, the generally valid facts confirming the increased concentrations of IL-1, TNF-alpha and LPS toxins in diabetics are induced by various types and families of chemokines (mainly IL-8), rather than by increased migration and selective transformation of neutrophils (8).

Increased concentrations of inflammation-inducing cytokines and markers significantly contribute to excessive pro-inflammatory state of the whole organism. In such a situation, a model associated with obesity and metabolic syndrome is relevant. It leads to the development of insulin resistance and to stimulation of adipocytes that produce free fatty acids (FFA), TNF-alpha, CRP, IL-1, and MCP-1. Inflammation-inducing cytokines, predominantly TNF-alpha, are considered important etiopathogenetic factors in the development of insulin resistance. In cooperation with LPS-toxin of gram-negative bacteria, the cytokines stimulate NF-kappaB, which after being transferred into the cell nuclei can trigger insulin resistance (1, 9).

Patients with abdominal type of obesity exhibit increased serum levels of TNF-alpha, which drop after reduction of body weight (10). Increased levels of TNF-alpha and other inflammation-inducing mediators in blood stream of patients with metabolic syndrome can stimulate the inflammation of periodontium, where also in clinically healthy subjects gram-negative anaerobic bacteria can be present and thus initiate the increase in proteolytic and osteolytic modes of destruction of these tissues (9, 11). The increased prevalence of periodontal diseases in obese people, mainly in younger subjects was confirmed also by NHANES III study, which encompassed 13,655 patients exam-

ined with periodontal indices (PD, AL) and BMI and WC indices. The association between these diseases was established using two different multivarious logistic regressive models containing other risk factors of periodontal diseases (sex, race, education, smoking, date of the last visit at the dentist) (12). Nowadays the secretory activity of adipocytes of fat tissue is considered a chronic low level of inflammation and an important inflammation-inducing etiopathogenetic factor of numerous serious diseases, including diabetes of type II and inflammatory destructive diseases of periodontium (1, 13).

The disorders of immune reaction, changes in microvasculature, defective bone reconstruction as well as osteoporotic changes in diabetic patients are often connected with damaged morphogenesis of the bone and osseous integration of dental implants (14). Applying this knowledge in implantological practice encourages us to reduce the indication range in these patients.

Non-enzymic glycemias is a chemical reaction, by which glucose is bound to amino acid of lysine residues and so-called Advanced Glycosylation Endproducts (AGEs) are formed by means of unstable up to more stable intermediate products. The formation and accumulation of AGEs runs also in periodontal tissues where they can influence their composition and immune defensive characteristics in several possible ways. In standard glycemic regime, a small amount of receptors (RAGEs) for AGEs are present in monocytes, smooth muscle cells, neurons, fibroblasts and endothelial cells. In patients with DM, increased amounts of RAGEs can lead to hyperproduction of adhesive molecules and oxidative substances. The latter hyperproduction results in an increased uncontrolled anti-inflammation immune response to the presence of microbial pathogens in the periodontium (15).

An important factor of an inappropriate antiinflammatory reaction is an excessive activity of proteolytic enzymes destroying soft tissue of the periodontium. Several studies have confirmed an increased concentration of metalloproteinases in the periodontium of diabetics. This is caused by their increased transcription of locally residing cells stimulated by an overproduction of inflammation-inducing cytokines (16). However, glycemias of collagen results in strengthening the transverse binding among its molecules and thus in decreasing its solubility, natural homeostasis and biological repairing qualities. Regeneration of ageing collagen and basal membranes is slowed down, and AGEs products accumulate in these structures (17). The destruction of periodontium is proportional to the unbalanced glycemic curve as well as to the level of glycemic hemoglobin.

In diabetic patients with HbA1c level higher than 8 per cent, the concentration of IL-1beta was twice as high as in patients with HbA1c lower than 8 per cent (18). The level of glycemic control and length of diabetic disease influence the grade of glycation and restoration of collagen in soft and osseous tissues, while the disorders in differentiation of osteoblasts and altered formation of extra-cellular matrix also contribute to this process (8, 19). Based on the mentioned studies, we can summarize that glycation of different tissue components of the periodontium

expressively alter its resistance against various exogenous agents (bacteria, viruses) and significantly decrease the remodeling, repair and healing of these tissues.

Oxidation stress represents a disorder in the balance between reactive radicals of oxygen (hydroxyl ion, superoxide, hydrogen peroxide) and antioxidant substances. An increased oxidation damages the proteins, DNA and lipids, while activating the anti-inflammatory cytokines and NF- κ B. In diabetic patients, in polyol way, glucose is being oxidized into sorbitol by means of aldoreductase while sorbitol is being further metabolized by means of sorbitoldehydrogenase into fructose. All these reactions run with active participation of NADPH. An increased production of reactive radicals of oxygen is etiopathogenically evoked by persistent hyperglycemia and increases the tissue insulin resistance. Nowadays, there is an accumulation of evidence that oxidants can originate also from excessive activation of NADPH oxidase, which is controlled with protein C kinase. The increased production of oxidants can run in phagocytic neutrophils but also in other resident cells (20).

In the past, **microbial factors** were significantly emphasized because some studies indicated specific subgingival microflora of some species, namely *Prevotella intermedia* and those of Capnocytophagic family. The today's state of knowledge based on several studies puts that there is no difference in distribution of individual bacterial pathogens in non-diabetic patients and diabetic ones with periodontitis, even if the patients with DM are afflicted with repeating infectious diseases (21).

Influence of periodontitis treatment to glycemic control and other parameters of DM

Acute and chronic infections unfavorably influence the course of glycemic curve and other clinical parameters of the diabetic illness. Chronic infections include also gram-negative infections of sub-gingival spaces connected with osteolysis and proteolysis of tissues of the periodontium and a significant formation of anti-inflammatory cytokines and immunologically active substances acting as stimulants to the anti-inflammatory immune response. The chronic infection of periodontium can increase the insulin resistance and clinical parameters associated with it (8). Nevertheless, it needs to be stated that despite the fact, that 44 out of 48 published interventional reviews and other studies have been proved to document the influence of diabetes on the development of inflammatory disease of periodontium, no general consensus has been achieved about the influence of periodontal therapy on the course and clinical parameters of diabetics (22). This discrepancy between periodontitis treatment and clinical parameters in diabetic patients can be caused by several factors such as composing heterogeneous groups of patients as to the type of diabetes, stage, and clinical course of periodontal affliction, disharmony in therapeutic procedures described in individual studies (applied/not applied antibiotics), heterogeneous level of metabolic control of patients and other factors mainly including the time factor.

In the light of numerous interventional and meta-analytical studies evaluating the effects of periodontal treatment on the course and glycemic values and other clinical parameters of diabetics, it is necessary to indicate that the beneficiary effect of non-surgical periodontological treatment both with and without application of antibiotics in patients of DM type 2 was based on reduction of periodontal pockets, and decrease in HbA1c levels in both groups, while the benefit was statistically important only in the groups with no antibiotics applied (23).

In spite of different variations and limitations, the Taylor's review study composed of twelve publications of MEDLINE database brings out evidence of improved glycemic control in diabetics after the treatment of infection in periodontal region. It stresses the importance of clinical and therapeutic care of patients with DM (24). Kiran et al. observed an effect of a therapeutically improved periodontal state on metabolic control in diabetics of type 2, whereby several periodontological and diabetological indices and parameters were observed; e.g. fasting plasma glucose (FPG), two-hour post-prandial glucose (PPG), HbA1c and cholesterol in a three-month time gap, when no periodontological treatment was applied in patients of the control group (25). Another study observes a group of older patients aged between 55 and 80 years suffering from DM of type 2 and a severe form of periodontitis and HbA1c level between 7.5 and 11.00. The applied therapy was based on mechanical deputation of periodontium and systemic application of doxycycline. After three months, an evaluation was done and a statistically important improvement of periodontal state and reduction of FPG and HbA1c values was stated. Nevertheless, this reduction was of no statistically important significance (26). On the other hand, a serious meta-analytic study consisting of ten interventional research works stated that HbA1c levels dropped after periodontal treatment totally in 0.38 %, in DM type 2 in 0.66 % and in applied antibiotics (doxycycline) in 0.71 %. No statistically important drop in HbA1c was noted (27). Based on the fact that the application of a relatively preferred combination of amoxicillin clavulanic acid caused also a significant reduction in HbA1c, one can assume that also the choice of antibiotics can play a crucial role (28). Other nine studies submitted for meta-analysis stated that periodontological treatment could lead to a statistically important reduction in HbA1c (29). Positive post-therapeutic results brought about a study enriched by identification of some parodontopathic bacteria. This study also stated that glycemic parameters in diabetic patients were influenced by the presence of *Porphyromonas gingivalis* with fimbriae of type II (30).

Following the effects of mechanical deputation and administration/non-administration of doxycycline proved not only a statistically important improvement in periodontological parameters but also a significant reduction in IL-6, interferon-inducible protein 10, granulocyte colony-stimulating factor. At the same time, also a reduction in HbA1c was observed, and paradoxically a significant improvement was noted in a group treated without antibiotics (31). Periodontological therapy significantly reduced also numerous cell populations and inflammatory markers associated with atherosclerotic complications in diabetic pa-

tients. Thus for instance, CD14+/blood monocytes dropped by 47 %, macrophages producing TNF-alpha decreased by 78 %, however lymphocytes producing interferon-gamma were not notably changed from the statistic viewpoint. Out of inflammation-inducing markers, CRP dropped by 37 % and the soluble E-selectin by 16.6 %. This indicates an inflammation reduction derived from monocyto-macrophagic population (32). Another pilot study has proved no statistically important improvement of pro-inflammatory mediators such as TNF-alpha and IL-6 after classical mechanical treatment of periodontium by means of instruments (33).

It is worth noticing that the concentrations of some growth factors such as VEGF (Vascular Endothelial Growth Factor) were similar in healthy individuals as well as in patients with DM. A good metabolic control had no influence on their concentrations in tissues, which can mean that some regeneration mechanisms mediated through VEGF can be preserved in patients with MD and destructive periodontitis (34).

Conclusion

Diabetes mellitus is an important etiopathogenetic factor responsible for the development and course of diabetic periodontitis. This confirms also a statistically important increase in the prevalence as well as in the pro-inflammatory state of the whole organism. Hyperglycemia alters the periodontal tissues by means of several mechanisms. Primary and at the same time well-researched factors include disorders of immune-defensive mechanisms, non-enzymatic glycemia of tissues and increased oxidative stress. However, this association does not function exclusively in one way because the diabetic periodontitis significantly modifies the clinical course of the whole disease, glycemic curve, insulin therapy and the amount of HbA1c.

It is necessary to note that some important growth factors e.g. VEGF were not changed or influenced by the presence of diabetic disease. The reversibility of the disease forces us to improve the management of total treatment of DM and establishes the necessity to cooperate between diabetologists and parodontologists or stomatologists. The introduced evidence provides us with sufficient reasons to suggest cooperation between diabetologists and stomatologists.

I. From the viewpoint of diabetologists, the glycemic curve, HbA1C and other biochemical parameters of DM should be continuously controlled because hyperglycemia influences unfavorably the anti-inflammatory defense response, and oxidative stress of microvascularity disorder in periodontal tissues, which in turn statistically significantly influences the development and course of diabetic periodontitis.

II. From the viewpoint of stomatologists, it is necessary to keep a permanent record of patients with diabetic periodontitis, subsequent depuration of subgingival spaces as well as a systemic and local medicamentous treatment. Through elimination or mineralization of the amount of periodontal bacterial pathogens in the periodontium, the intensity of inflammation decreases while the state of the whole organism improves. This influences positively also the whole course of DM.

III. The latest knowledge is very important for the indication of implantological treatment in diabetic patients because in diabetic patients of type II, there were diagnosed disorders of microvascularisation and reduced bone reconstruction with a successive disorder of osseous integration in the implant area. These complications of implantological therapy can be enhanced with the presence of secondary DM osteoporosis.

References

1. King GL. The role of inflammatory cytokines in diabetes and its complications. *J Periodontol* 2008; 79 (Suppl 8): 1527–1534.
2. Andersen CCP, Flyvbjerg A, Buschard K, Holmstrup P. Relationship between periodontitis and diabetes: Lessons from rodent studies. *J Periodontol* 2007; 78 (7): 1264–1275.
3. Ceriello A. Postprandial hyperglycemia and diabetes complications. Is it time to treat? *Diabetes* 2005; 54 (1): 1–7.
4. Strauss SM, Wheeler AJ, Russell SL. The potential use of gingival crevicular blood for measuring glucose to screen for diabetes: An examination based on characteristic of the blood collection site. *J Periodontol* 2009; 80 (6): 907–914.
5. Tsai C, Hayes C, Taylor GV. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. *Comm Dent Oral Epidemiol* 2002; 30: 182–192.
6. Dakovic D, Pavlovič MD. Periodontal disease in children and adolescent with type 1 diabetes in Serbia *J Periodontol* 2008; 79 (6): 987–992.
7. Donahue RP, Wu T. Insulin resistance and periodontal disease: An epidemiologic overview of research needs and future directions. *Ann Periodontol* 2001; 6: 119–124.
8. Maley BL, Oates TW. Diabetes mellitus and periodontal diseases. AAP-Commissioned review. *J Periodontol* 2006; 77: 1289–1303.
9. Nishimura F, Iwamoto Y, Mineshiba J, Shimizu A, Soga Y, Murayama Y. Periodontal disease and diabetes mellitus: The role of tumor necrosis factor- α in a 2-way relationship. *J Periodontol* 2003; 74: 97–102.
10. Dandona P, Weistock R, Thusu K. Tumor necrosis factor- α in sera of obese patients: Fall with weight loss. *J Clin Endocrinol Metab* 1998; 83: 2907–2910.
11. Wolff LF, Aepli DM, Pihlstrom BL. Natural distribution of five bacteria associated with periodontal disease. *J Clin Periodontol* 1993; 20: 699–706.
12. Al-Zahrani MS, Bissada NF, Borawski A. Obesity and periodontal disease in young, middle-aged, and older adults. *J Periodontol* 2003; 74: 610–615.
13. Ferenčík M, Hulín I. Obezita, tukové tkanivo a zápal. *Med Monitor* 2008; 4: 1–6.
14. Wang F, Song Y-I, Li D-h. Type 2 diabetes mellitus impairs bone healing of dental implants in GK rats. *Diab Res Clin Pract* 2010; doi: 10.1016/j.diabetes.2010.01.017.
15. Verma S, Bhat KM. Diabetes mellitus – a modifier of periodontal disease expression. *J Int Acad Periodontol* 2004; 6: 13–20.
16. Kumar MS Vams G Sripriya R Sehgal PK. Expression of matrix metalloproteinases /MMP-8 and 9/ in chronic periodontosis patients with and without diabetes mellitus. *J Periodontol* 2006; 77: 1803–1808.

- 17. Rybka J.** Neenzymatická glykace a její význam v praxi. Praha; Avicenum, 1990: 56–76.
- 18. Engebretson SP, Hey-Hadavi J, Erhardt FJ et al.** Gingival crevicular fluid levels of interleukin-1beta and glycemic control in patients with chronic periodontitis and type 2 diabetes. *J Periodontol* 2004; 75: 1203–1208.
- 19. McCarthy AD, Etcheverry SB, Bruzzone L et al.** Non-enzymatic glycosylation of type I collagen matrix: effects on osteoblastic development and oxidative stress. *BMC Cell Biol* 2001; 2: 16–21.
- 20. Nassar H, Kantarci A, Van Dyke TE.** Diabetic periodontitis: a model for activated innate immunity and impaired resolution of inflammation. *Periodontol* 2007; 43: 233–244.
- 21. Ebersole JL, Holt SC, Hansard R, Novak MJ.** Microbiologic and immunologic characteristics of periodontal disease in Hispanic Americans with type 2 diabetes. *J Periodontol* 2008; 79: 637–646.
- 22. Lambles F, Silvestre FJ, Hernandez-Mijares A, Guiha R, Cafesse R.** The effect of periodontal treatment on metabolic control of type 1 diabetes mellitus. *Clin Oral Invest* 2008; 12: 237–343.
- 23. Rodrigues DC, Taba MJ, Novaes AB, Souza SL, Grisi MF.** Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. *J Periodontol* 2003; 74: 1361–1367.
- 24. Taylor GW.** The effects of periodontal treatment on diabetes. *J Am Dent Ass* 2003; Spec No: 41S–48S.
- 25. Kiran AU, Arpak N, Unsal E, Erdogan MF.** The effect of improved periodontal health on metabolic control in type 2 diabetes mellitus. *J Clin Periodontol* 2005; 32: 266–272.
- 26. Promsudthi A, Pimapsri S, Deerochanawong C, Kanchanasita W.** The effect of periodontal therapy on uncontrolled type 2 diabetes mellitus in older subjects. *Oral Diseases* 2005; 11: 293–298.
- 27. Janket SJ, Wightman A, Baird AE, Van Dyke TE, Jones JA.** Does periodontal treatment improve glycemic control in diabetic patients? A meta-analysis of intervention studies. *J Dent Res* 2005; 84: 1154–1159.
- 28. Débora CR, Taba M Jr, Novaes AB Jr, Souza SLS, Grisi MFM.** Effect of non-surgical periodontal therapy on glycemic control in patients with type 2 diabetes mellitus. *J Periodontol* 2003; 74: 1361–1367.
- 29. Darre L, Vergnes JN, Gourdy P, Sixou M.** Efficacy of periodontal treatment on glycaemic control in diabetic patients: A meta-analysis of interventional studies. *Diabet Metabol* 2008; 34: 497–506.
- 30. Makiura N, Ojima M, Kou Y, Furuta N, et al.** Relationship of Porphyromonas gingivalis with glycemic level in patients with 2 diabetes following periodontal treatment. *Oral Microb Immunol* 2008; 23: 348–51.
- 31. O’Connell PA, Taba M, Nomizo A, et al.** Effects of periodontal therapy on glycemic control anti-inflammatory markers. *J Periodontol* 2008; 79: 774–783.
- 32. Lalla E, Kaplan S, Yang J, Roth GA, Papanou PN, Greenberg S.** Effects of periodontal therapy on serum C-reactive proteins, E-selectin, and tumor necrosis factor-alpha secretion by peripheral blood-derived macrophages in diabetes. A pilot study. *J Periodontol Res* 2007; 42 (3): 274–282.
- 33. Talbert J, Elter J, Jared HL, Offenbacher S, Southerland J, Wilder RS.** The effect of periodontal therapy on TNF-alpha, IL-6 and metabolic control in type 2 diabetics. *J Dent Hyg* 2006; 80: 7.
- 34. Keies GC, Cetinkaya BO, Eroglu CE.** Vascular endothelial growth factor expression levels of gingiva in gingivitis and periodontitis patients with/without diabetes mellitus. *Inflamm Res*; DOI 10. 1007/s0001-010-0158-8.

Received March 10, 2010.

Accepted February 15, 2011.