Oral Alterations in Diabetes Mellitus

SUMMARY

Diabetes mellitus is one of the most common chronic diseases which continue to increase in number and significance. It presents the third most prevalent condition among medically compromised patients referring for dental treatment. Diabetes mellitus has been defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Hyperglycemia leads to widespread multisystem damage which has an effect on oral tissue. The present article summarizes current knowledge regarding the association between diabetes mellitus and oral and dental health.

Key words: Diabetes Mellitus, Oral Disease, Oral Health

Classification and epidemiology of diabetes mellitus

Diabetes mellitus is defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both according to American Diabetes Association. Although number of different classification of diabetes has been proposed, current classification is based upon the disease etiology. Type 1 diabetes, characterized by the lack of insulin production resulting in severe hyperglycemia and ketoacidosis and includes immune mediated diabetes and idiopathic diabetes (5-10% of diabetic populations).

Type 2 diabetes is characterized by insulin resistance mainly by altered insulin production but with certain capacity for insulin production without autoimmune destruction of β-cells (90-95% of diabetic population). Risk factors for this form of diabetes are overweight, obesity and age. It is more common in women with history of gestational diabetes mellitus and in those with hypertension or dyslipidemia. Type 2 diabetes commonly remains undiagnosed for a long time as hyperglycemia appears gradually and often without symptom, while ketoacidosis seldom occurs.

Gestational diabetes mellitus refers to glucose intolerance of variable severity which is identified during pregnancy for the first time, regardless of possibility that the glucose intolerance may antedate pregnancy. Gestational diabetes significantly increases the risk for later development of type 2 diabetes mellitus.

Other forms of diabetes mellitus are represented as genetic defects related to the β-cell or insulin action, exocrine pancreas diseases, diabetes secondary to autoimmune endocrinopathies, diabetes caused by drugs, chemicals, infections, rare forms of immune-mediated diabetes, and diabetes mellitus associated with genetic syndromes.

Diabetes mellitus presents one of the most frequent chronic diseases which continually grows in prevalence and significance. According to World Health Organization 171 million people had diabetes in 2000 and it is predicted that this number will increase to 366 million by 2030. Other estimate by International Diabetes Federation suggested that the prevalence was 381 million in 2013, and that the increase in worldwide numbers will be 592 million by 2035. These data indicate that the prevalence and incidence of diabetes mellitus is increasing, which could be attributed to demographic changes such as population growth and aging, or lifestyle change related to urbanization, as well as to the extended lifespan due to generally improved health of diabetic patients.
Diabetes mellitus induced complications

Hyperglycemia due to diabetes mellitus lead to generalized damage that affects multiple systems, particularly microvascular changes (microangiopathy) with thickening of the capillary basement membrane (includes retinopathy and nephropathy), macrovascular disease (macroangiopathy) with accelerated arteriosclerosis (includes coronary artery disease, cerebrovascular disease, and peripheral vascular disease), neuropathy affecting somatic and autonomic nervous system, and oral disease. Beside these chronic complications, diabetes could cause acute complications such as hyperosmolar hyperglycemia, diabetes ketoacidosis, and acute infection.

Microvascular changes are hallmark of many diabetic complications. Sustained hyperglycemia induces production of advanced glycation end products (AGEs) from proteins and lipids. AGEs are considered to stand in the basis of a variety of diabetic complications. AGEs often form on collagen, which precipitates in large blood vessels walls, and cause accumulation of low-density lipoprotein, thus contributing to atherosclerotic changes (macrovascular complications). AGE-modified collagen also plays a role in thickening the basement membrane in the small blood vessels leading to alterations in homeostatic membrane transport. AGEs formation and microvascular complications have been associated with elevated level of vascular endothelial growth factor (VEGF). AGEs receptors (RAGE) have been found on the surfaces of smooth muscle cells, endothelial cells, fibroblasts, neurons, lymphocytes and monocytes/macrophage. Hyperglycemia increases expression of RAGE while AGE-RAGE interaction on monocytes induces an oxidative stress and the activation of nuclear factor kappa B (NF-kB) and consequently increases the secretion of proinflammatory cytokines including interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α). Increased production of these mediators is recognized as critical in the inflammatory process. AGE-RAGE interaction on endothelium enhances vascular permeability and thrombus formation. Vascular problems cause increased risk for infection, as well as its severity and duration due to reduced oxygen diffusion across the capillary wall, neutrophil microbicidal suppression and failure in delivering humoral and cellular components of the immune system. Changes in collagen metabolism are common findings in diabetic. As a consequence, synthesized collagen is rapidly degraded by higher level of matrix metalloproteinase (MMP), while AGE-modified collagen accumulates in the tissue, altering wound healing. Diabetes has a negative impact on bone healing by reducing the expression of genes responsible for differentiation of the osteoblasts and by decreasing growth factor and extracellular matrix production.

Oral complications in diabetes mellitus

Salivary findings

Xerostomia, altered saliva secretion and composition, taste impairment, and burning sensation are common oral complications related to diabetic salivary glands.

Xerostomia

Xerostomia is defined as the subjective complaint of the oral dryness that implies change in the salivary composition and/or flow rate. Patients with type 1 and type 2 diabetes mellitus complain of xerostomia more frequently than healthy controls. Estimated global prevalence of xerostomia among diabetic patients ranges between 34%-51%. Symptoms of dry mouth in type 2 diabetic patients have been linked with peripheral neuropathy. Nevertheless, this association has not been confirmed for type 2 diabetes patients. Recent animal study provided evidence that alterations in nitric oxidedihydrorbioprotein production correlate with reduced salivation and increased water intake, a typical symptom of xerostomia. Higher rates of xerostomia were related to the female sex in type 2 diabetic patients, but to xerogenic medication, current use of cigarettes, and more frequent snacking behavior in type 1 diabetic patients. Glycemic control level seems to generally influence the susceptibility of type 2 diabetes to xerostomia.

Salivary flow

Findings of salivary flow rates among patients with diabetes are conflicting. Some studies have shown lower resting and/or stimulated salivary flow in both type 1 and 2 diabetes mellitus, whereas other authors have found no differences between diabetic patients and controls. Decrease in salivary flow in type 2 diabetic patients is less severe compared to type 1 diabetes. Some authors contend that hyposalivation is related to increased blood glucose concentration. Namely, dehydration linked to increased blood glucose may enhance osmotic gradients in gland and thus decrease salivary secretion. Besides, decreased salivary flow in type 1 or type 2 diabetes has been associated with poor control of diabetes, xerogenic medication, presence of peripheral neuropathy, and obesity–insulin resistance.

Recently, it has been hypothesized that beside hyperglycemia, decreased salivary secretion might be induced by dyslipidemia and hyperinsulinemia which give rise to oxidative stress, inflammation, sympathetic activity, and alter insulin signaling in the salivary gland, eventually resulting in gland degradation. Furthermore, findings of another recent publication suggest that salivary gland hypofunction in type 2 diabetes patients might be associated with genetic polymorphisms of chromogranin A, secretory glycoprotein which is supposed to give
concentrations of certain salivary elements varied in increased, while zinc ions were decreased. Furthermore, magnesium, and potassium ions were found to be stimulated concentrations of salivary proteins, calcium, and acidic pH of resting saliva. In addition, resting and concentration of total sugars, glucose, α-amylase, urea, infections among diabetes patients may play a role in predisposition to the dental calculus while more calcium and less zinc ions in the saliva to higher susceptibility of diabetics to the dental caries levels of glucose and decreased pH in saliva were linked to the salivary hypofunction, or that the primary tastes22 show altered taste sensations including hypogeusia for healthy controls14. These disturbances include higher thresholds were observed in the facial areas innervated by trigeminal nerve and they were positively correlated with the trigeminal nerve and they were positively correlated. In other words, it seems that duration of disease, age, and sex do not affect salivary flow rates in patients with type 2 diabetes. Decreased salivary gland function has been reported to be incriminated in the pathogenesis of candidiasis17, and associated with the increased risk of dental caries8,17 and periodontitis18.

Sialosis
In certain percent, patients with long history of diabetes may develop sialosis19. Tis pathology comprises bilateral, painless, non-inflammatory, non-neoplastic, but degenerative glandular enlargement, which usually affects parotid glands. It is related to an alteration in the neuro-anatomic regulation of the gland due to demyelinization and consequent atrophy of the mioepithelial cells20. Hystopathologically, increase in glandular size is characterized by fatty infiltration of the stroma, ductal dilatation, and reduced size of the acini. According to the more recent reports, benign parotid hypertrophy might be related to the enlargement of acinar cells, probably as a result of an interruption in the protein synthesis and release19. It has been stated that the enlargement is accompanied by the salivary hypofunction, or that the salivary function is generally preserved.

Salivary composition
Composition of saliva has also been examined and certain changes in the quality have been observed in both type 1 and type 2 diabetics in comparison to the healthy controls14. These disturbances include higher concentration of total sugars, glucose, α-amylase, urea, and acidic pH of resting saliva. In addition, resting and stimulated concentrations of salivary proteins, calcium, magnesium, and potassium ions were found to be increased, while zinc ions were decreased. Furthermore, concentrations of certain salivary elements varied in diabetics and healthy individuals regarding to the sex14. It has been hypothesized that microvascular changes and neuropathy may play a role in these changes12. Higher levels of glucose and decreased pH in saliva were linked to higher susceptibility of diabetics to the dental caries while more calcium and less zinc ions in the saliva may play a role in predisposition to the dental calculus formation and periodontitis in diabetic patients. Diabetes mellitus was associated with decrease in the secretion of immunoglobulin A suspected of influencing propensity to infections among diabetes patients.

Taste impairment
It has been previously reported that diabetic patients show altered taste sensations including hypogeusia for the primary tastes22. Among the patients with diabetes or prediabetes, about 6% showed changes in sweet taste perception and about 9% showed salt taste disorder23. Taste impairment may impede the maintenance of a proper diet, because of the loss of the sweet and salty taste sensation, with favoring sugary and/or salty food20,22. These changes are generally tolerated without complaint, and significantly associated with the complications and duration of diabetes. Namely, consumption of the large amounts of sugar and sodium, may rapidly enhance blood glucose level and hypertension21. A neuropathic mechanism, as well as the dryness of mucosa, decreased gustin production, zinc deficiency and coated tongue24 has been suggested to explain alteration in taste. Moreover, changes in sweet taste perception might be related to the general impairment in the sweet taste receptor, associated with low glucagon-like peptide 1 (GLP-1) secretion25 and enhanced glucose absorption26.

Burnning sensation
Diabetes mellitus, especially if uncontrolled, might be associated with the burning sensation in the oral mucosa27. In addition, diabetes control results in the improvement of oral burning28. Burning sensation in diabetic patients has been attributed to poor glycemic control, metabolic alterations in oral mucosa, angiopathy, candidiasis and regional neuropathy28. The neuropathic pain in diabetic patients has been reported as burning, tingling, or even as electric shock or stabbing sensation and present one of the most disabling symptoms in patients suffering from the painful diabetic neuropathy29. Painful diabetic neuropathy has been linked to the pain perception generated by a stimulus that does not usually provoke pain (allodnya) and increased response to painful stimuli (hyperalgesia)30. These pain sensations have a considerable and detrimental impact on the physical and psychological functioning, and correlate with the level of sleep disturbance, anxiety and depression31.

Other oral symptoms observed in the poorly controlled diabetics related to the diabetic neuropathy, comprise pain related clinical conditions such as trigeminal pain and temporomandibular joint disorder.

Orofacial Pain
Available findings suggest that the oral nerve pain might be related to diabetic polyradiculopathy. Arap et al.32 explored the oral symptoms and facial somatosensory signs in patients with extraoral complications of painful diabetic neuropathy. According to their results, the majority (55 %) of the patients reported the orofacial pain, and the mean pain intensity was 5.6 by the visual analogue scale (VAS). Patients described the pain as fatigue (50%), throbbing, sensitive and queasy (about 43% each), bothering (about 36%), or twinge, pinch and aching (approximately 28% each). In addition, higher pain thresholds were observed in the facial areas innervated by the trigeminal nerve and they were positively correlated.
with the higher levels of glycated hemoglobin. Neuralgia in the orofacial region in conjunction with diabetes is rarely reported. However, in a diabetic woman, severe oral pain provoked by touch in the mandible area, tongue and gingival region have been observed, which led to the assumption of the involvement of the mandibular branch of the trigeminal nerve.

Although the data are scarce, there are certain indicators that suggest there is an association between diabetes and temporomandibular disorders (TMD). A study in Finnish population reported TMD in 27% of type 2 diabetic patients and in 16% of controls. In addition, peripheral and autonomic parasympathetic neuropathies were identified as independent risk factors for temporomandibular dysfunction. According to the results obtained in another study, the prevalence of TMD in the group of participants with diabetes mellitus type 2 and the neuropathic pain in peripheral diabetic neuropathy was similar to the values reported in general population, and the majority were classified as non-painful TMD diagnosis. These findings need to be clarified in the future studies.

**Periodontal disease**

Diabetes has been described as a risk factor for periodontal disease. Although the majority of researches have focused on type 2 diabetes, type 1 diabetes appears to have an identical effect on periodontitis occurrence risk. Some young diabetic people develop periodontitis, but periodontal disease is much more common in diabetic adults. Diabetes may influence not only the prevalence but also severity and progression of periodontitis. Recent evidence reported increasing periodontitis prevalence with increasing levels of blood glucose in type 2 diabetes, namely, 19.2, 33.9, 46.3, 53.3, and 62.5% persons with periodontitis, apropos, in person with normal glucose level, prediabetes, newly detected diabetes, well-controlled (HbA1c<7.0%), and poorly-controlled (HbA1c≥7%) persons. In addition, in uncontrolled diabetics both type 1 and type 2 periodontal destruction was more severe, with greater mean bone loss, attachment loss and tooth loss. However, there is no unequivocal dose-response relationship between glycemia and periodontitis.

There is a wide range of mechanisms by which diabetes adversely affects the periodontium. These mechanisms are not entirely understood but involve aspects of inflammation, immune functioning, neutrophil activity and cytokine biology. The microbial composition of the subgingival biofilm between nondiabetic patients and those with type 1 and type 2 diabetes exhibit subtle differences, but clinical relevance of this is not clear. The immune response to periodontal bacterial infection differs in diabetics by means that they do not develop antibodies to periodontitis associated pathogens. Both type 1 and type 2 diabetes are associated with elevated levels of systemic markers of inflammation. Diabetes increases inflammation in periodontal tissues and people with type 2 diabetes have higher levels of inflammatory mediators such as IL-1β, TNF-α, interferon-γ (IFNγ), osteoprotegrin (OPG), IL-17 and IL-23, but also exhibit a downregulation of IL-4. There is a possible role for type 2 diabetes in modulating the level of receptor activator of NF-kB ligand (RANKL)/(OPG) in chronic periodontitis. A limited number of studies have investigated the role of adipokines in periodontal disease and diabetes. Kardesler et al. found no effect of type 2 diabetes on serum leptin and adiponectin in chronic periodontitis, while in another study serum adiponectin was elevated in type 1 diabetes patients with chronic periodontitis. Pradeep et al. showed a possible association between pre-B-cell colony enhancing factor (Visfatin) and type 2 diabetes in chronic periodontitis patients. Also, neutrophil function is altered in the diabetic patients. Oxidative stress in diabetes may activate periodontium pro-inflammatory mechanisms which could influence diabetes.

On the other side, there is an evidence to support a negative impact of periodontal disease on diabetes and much emphasis on the two-way relationship between these two diseases has been given. While diabetes significantly impacts the periodontium, there is also evidence that periodontitis may promote development of type 2 diabetes. Also, periodontal disease adversely affects glycemic control. Ulcerated pocket epithelium could constitute a chronic source of systemic challenge for bacterial products and locally produced inflammatory mediators such as TNF-α, IL-6 and IL-1 due to predominance of gram-negative anaerobic bacteria in periodontal infection. All these important periodontal inflammation mediators are reported to antagonize insulin action. Increased insulin resistance and poor glycemic control may occur as a consequence of chronic gram-negative periodontal infections. In addition, periodontitis increase the risk for diabetic complications. The prevalence and severity of non-oral diabetes related complications such as retinopathy, diabetic neuropathy, proteinuria and cardiovascular complications are reported to be correlated with the severity of periodontitis. The classic complications of diabetes may be closely associated with the periodontal disease, which lends further credence to the concept that periodontal disease may be the sixth complication of the diabetes.

Intervention trials are of the most importance for determining the influence of the periodontal diseases on diabetes. The impact of periodontal therapy on glycemic control is often related to the changes in periodontal health after treatment. The changes in glycemic control may reflect changes in the gingival inflammation level. Recent systematic review and meta-analysis evaluating the effect of periodontal therapy on the outcome of diabetes in patients with type 2 observed moderate
reduction in HbA1c\(^{49}\). Another review including patients with type 1 and type 2 diabetes showed that there is low evidence that the periodontal treatment by scaling and root planning improves glycemic control in people with diabetes, with a mean percentage reduction in HbA1c of 0.29\% at 3-4 months\(^{50}\). In addition, the authors found no evidence showing that one periodontal treatment is more effective than another in improving glycemic control\(^{49}\). Therefore, larger, well conducted prospective studies are required to elucidate the effect of periodontal treatment on glycemic control of the patients with diabetes.

**Oral mucosa alterations**

Diabetes mellitus was associated with several specific oral mucosa alterations although these associations have not been found to be consistent in all subjects with diabetes\(^{51}\). There are reports of higher incidence of development conditions, such as coated and fissured tongue, benign migratory glossitis, melanin pigmentation and varices\(^{52}\). Also, diabetic patients are more prone to fungal infection\(^{53}\) and potentially malignant disorders including leukoplakia, erythroplakia\(^{54}\), and lichen planus\(^{55}\). Susceptibility of diabetic patients to alteration and infection in oral cavity is still debated but inadequate control of diabetes, immunological alteration, microcirculatory changes with reduction of blood supply, xerostomia and alteration in salivary flow and composition and smoking was mentioned\(^{4,54}\).

**Dental tissue alterations**

**Dental pulp changes**

Chronic hyperglycemia may cause irreversible changes in pulp tissue leading to pulp necrosis. Histological studies showed reduction in the concentration of collagen and fibroblast, increased thickness of blood vessel basement membrane, angiopathy and calcification\(^{55,56}\). Increased presence and activity of inflammatory components, such as kallikrein and myeloperoxidase, with progressive deterioration of the matrix components were observed in diabetic rats after 30 and 90 days of streptozocin treatment\(^{55}\). In another study an increasing trend in inflammatory cells volume density was found in the diabetic rats at 1 and 3 months of diabetic induction, with necrosis areas after 3, 6, 9, and 12 months\(^{56}\). Also, diabetes modifies the parameters of the antioxidant system in rat pulp tissue, by increasing catalase activity and reducing sialic acid concentration, which indicates that diabetic pulp could have impaired response to AGEs and reactive oxygen species\(^{57}\). Increased level of BMP2 and VEGF in healthy teeth and their decreased level in teeth with indirect pulp capping were observed in diabetic human pulp tissue\(^{58}\). Diabetes mellitus may interfere with dental pulp healing. Inhibition of dentin bridge formation and an increase in pulp inflammation was observed after pulp caping procedures in rats with streptozocin induced diabetes mellitus\(^{59}\).

**Dental caries**

The findings regarding relationship between diabetes and coronal or root caries are not conclusive. In experimental models, prevalence and severity of dental caries is increased in diabetic animals and the poor metabolic control contributes to increased caries rate\(^{56}\). Another study denies such correlation\(^{60}\). Many cross-sectional clinical studies found higher prevalence of dental caries for subjects with diabetes both type 1\(^{59}\) and type 2\(^{62,63}\). Also, positive correlation of caries with duration of diabetes\(^{62,63}\), type of diabetes\(^{62}\) and metabolic control has been reported\(^{62,63}\). On the contrary, a number of authors have not found the correlation between dental caries and diabetes, type of diabetes, duration of disease, metabolic control and the existence of diabetic complications\(^{64}\). The mechanisms by which diabetes could affect prevalence and incidence of dental caries are still debated, but reduced salivary flow, increase of carbohydrate in the saliva, increased level of oral yeasts, *Mutans streptococci* and *Lactobacilli* are some of the factors considered to play a role\(^{17}\).

**Apical periodontitis**

Animal studies showed more pronounced periapical inflammation, larger periapical lesion and greater root and alveolar bone resorption in diabetic rats compared to nondiabetic\(^{65}\). Human studies showed that the apical periodontitis was significantly higher in diabetic compared to nondiabetic individuals\(^{66,67}\), and that diabetic patients exhibit four times higher risk of apical periodontitis\(^{66}\). Furthermore, association between radiolucent periapical lesions and glycemic control of type 2 diabetic patients assessed by the mean HbA1c level was found\(^{67}\). Other found no association of diabetes with higher prevalence of apical periodontitis\(^{68}\). Recent systematic review was inconclusive regarding the relationship between diabetes mellitus and apical periodontitis prevalence\(^{69}\). Concerning the influence of diabetes mellitus on prevalence of root canal treated teeth, Lopez-Lopez et al.\(^{66}\) found that the likelihood of having at least one root filled was twice in diabetic patients than in nondiabetic subjects. Other failed to find association between diabetes mellitus or glycemic control in diabetic patients with prevalence of root filled teeth\(^{67}\). Several investigations studied the potential relationship between diabetes and root-filled teeth outcome and survival. The results of some studies showed that neither diabetes\(^{66}\) nor glycemic control in diabetes\(^{67}\) affected the endodontic outcome. On contrary, Fouad and Burleson\(^{70}\) found that patient with diabetes have a reduced likelihood of endodontic success in teeth with apical periodontitis comparing to controls, even after controlling for other risk factors. Significant difference in the prevalence of
root treated teeth with periapical radiolucencies between diabetics and controls have not been found, but males with type 2 diabetes presented higher risk of residual periapical lesions in the root filled teeth.\cite{luo2015beneficial}

Furthermore, diabetes contributes to decrease retention of root filled teeth. Recent systematic review and meta-analysis indicate significant association between diabetes and prevalence of periapical radiolucencies in root-filled teeth and recognize diabetes as an important pre-operative factor affecting the treatment outcome.\cite{cicmil2018association}

Chronic inflammation, reduced tissue repair capacity, impaired immune response, impaired bone turnover and delayed wound healing that have been found in diabetes may be responsible for periapical status of root filled teeth in diabetic patients.\cite{fuchs2016effects}

Relationship between infections of dental origin and systemic health has been investigated predominantly in subjects with periodontal disease. However, apical periodontitis is also capable of potentiating systemic inflammatory changes. Astolphi et al.\cite{astolphi2009} found that in non-diabetic rats apical periodontitis was able to cause alteration in the insulin signaling and insulin sensitivity, probably due to plasmatic TNF-α increase. Other found that oral infection and diabetes are associated to the changes in tryglyceride levels\cite{zhang2009elevated}, and that oral inflammation affects glycemic condition and increases HbA1c levels in diabetic animals.\cite{zhang2009inflammation}. Also, periapical and periodontal disease increase serum level of IL-17 in normoglycemic and diabetic rats, and levels of leucocytes, neutrophils and blood glucose concentration in the diabetic rats.\cite{zhang2009inflammation, zhang2009elevated}

**Conclusions**

Diabetes mellitus presents the third most prevalent condition among medically compromised patients referring for dental treatment. Diabetes causes multiple comorbidities and increase risk of systemic and oral complications. Various oral complications in diabetics might be dependent on type, duration and control of the disease. Thus, treatment goal is implementation of preventive and therapeutic measures for the management of both diabetes mellitus and oral complications. Concerning the fact that many individuals seeking dental care have undiagnosed diabetes and that early diagnosis is important in preventing or mitigating complications, oral findings may offer an opportunity for the identification of high-risk persons.

Namely, it has been shown that presence of 26% or more teeth with deep pockets (with probing depth \( \geq 5\text{mm} \)) or 4 or more missing teeth identified pre-diabetes or diabetes in 72% of cases. In patients with an increased risk, a blood test can be applied (HbA1c) at first appointment, which increases correct identification to 87%. Thus, dental professionals have the opportunity not only to diagnose and cure diabetic complications, but also to take active role in identifying those with undiagnosed hyperglycemia.

**References**


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