Salivary glands dysfunction and oral manifestations in diabetes and obesity - review

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A- Conception and study design; **B -** Collection of data; **C -** Data analysis; **D -** Writing the paper;
E- Review article; **F** - Approval of the final version of the article; **G** - Other (please specify)

ABSTRACT

Diabetes mellitus (DM) is a group of metabolic disorders of multiple etiologies characterized by hyperglycemia. In 2014 it affected approximately 422 million individuals worldwide. Unfortunately, it is associated with a set of co-morbidities that contribute to a significantly reduced, i.e. 5-10 years, life expectancy. The following review will discuss the most common long-term complications of diabetes. For practical reasons we decided to narrow our interests to its very widespread, even 90-95% of the cases, form - type 2 diabetes mellitus. During the discussion particular emphasis will be placed on the salivary glands function since previous investigation has confirmed its relation to many burdensome oral diseases, while the effective medical care over diabetic patients requires better understanding of pathomechanisms of its (i.e. diabetic) oral manifestations.

Keywords: Diabetes, obesity, hyperglycemia, oral complications, co-morbitidities

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DOI: 10.5604/01.3001.0012.1119

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Received: 12.01.2018
Accepted: 25.01.2018
Progress in Health Sciences
Vol. 8(1) 2018 pp 134-140

INTRODUCTION

Diabetes mellitus (DM) is a collective term for a group of metabolic disorders of multiple etiologies characterized by hyperglycemia (fasting plasma glucose level ≥ 7.0 mmol/L or 126 mg/dL) [1–3]. It occurs as a consequence of abnormalities in insulin secretion/action and is one of the most prevalent medical conditions nowadays [3]. In 2014 it affected approximately 422 million adults worldwide contributing to almost 3.7 million deaths yearly [4]. Interestingly, diabetes can be divided into four broad categories (Table 1), the first two (type 1 and 2) encompassing the vast majority of all its cases [4–6].

Type 1 diabetes is a common metabolic condition usually affecting children. Generally, it is distinguished by a rapid onset resulting from a loss of insulin secreting pancreatic β-cells [5]. Although its exact causes remain unknown the majority of them are associated with some sort of autoimmunological response (autoimmunological T1DM), with the remaining part being of no known origin (idiopathic diabetes). Unfortunately, its occurrence cannot be prevented based on the modern medicine therapies and the individuals require life-long insulin injections [4].

Type 2 diabetes, on the other hand, is a gradually developing condition affecting mostly adults. In comparison with T1DM it is characterized by a relative insulin deficiency caused by an

This situation is commonly attributed to modern lifestyle, i.e. wrong nutritional habits and/or insufficient physical activity. Indeed, the majority of patients with T2DM are obese, and obesity, especially the abdominal one, was shown to cause or aggravate insulin resistance [7–9]. Moreover, diabetic patients frequently do not adhere to therapeutic regime. A study of Kawahara et al. [10], for instance, showed that 57% of diabetic patients gave up their regular clinical follow-up visits, ordinarily excusing themselves with a busy schedule. Unfortunately, diabetes mellitus is associated with a set of comorbidities that contribute to a significantly reduced, i.e. 5-10 years, life expectancy [11].

Long-term complications of diabetes mellitus [3-4,11,19,20]: Retinopathy, Nephropathy, Neuropathy, Atherosclerosis, Dyslipidemia, Ischemic heart diseases/coronary heart disease, Stroke, Peripheral vascular disease, Erectile dysfunction, Hypertension and Non-alcoholic fatty liver disease

inadequate response of its target tissues (insulin resistance) [3,4,7]. Surprisingly, although its occurrence can be either prevented or delayed it is estimated to affect around 90% of diabetic patients [4].

Aetiological types of diabetes mellitus [1,3,4]

1. Type 1 diabetes mellitus (DM) ~ 5-10% of all the cases
    - Autoimmune
    - Idiopathic
2. Type 2 diabetes mellitus (DM) ~ 90% of all the cases
    - Predominantly of insulin resistance with relative insulin deficiency
    - Predominantly secretory effect with/without insulin resistance
3. Gestational Diabetes Mellitus (GDM)
4. Other types
    - Genetic defects of β-cells function
    - Genetic defects in insulin action
    - Diseases of the exocrine pancreas
    - Endocrinopathies
    - Drug- of chemical-induced diabetes
    - Infections
    - Uncommon forms of immune-mediated diabetes
    - Other genetic syndromes sometimes associated with diabetes

- Lower extremity amputations
- Oral diseases

Oral complications of diabetes mellitus and their prevalence in the population of diabetics [44]:

- Periodontitis ~34%
- Oral candidiasis ~24%
- Tooth loss ~24%
- Dental caries ~24%
- Mucosal ulceration ~22%
- Taste impairment ~20%
- Halitosis (fetor ex ore) ~16%
- Xerostomia ~14%
- Burning mouth syndrome ~10%

The following review will discuss the most common long-term complications of diabetes.

For practical reasons we decided to narrow our interests to its most prevalent (i.e. T2DM) form. Moreover, particular emphasis will be placed on oral diseases.

TYPE 2 DIABETES AND OBESITY – PATHOPHYSIOLOGY

Although the pathogenesis of type 2 diabetes is a complex and multi-factorial mechanism, still many researchers have pointed out on a connection between the size of a person's fat depots and insulin resistance (IR) as an underlying cause of the disease [7,12].

Obese people are characterized by a positive energy balance, which in the long run frequently exceeds adipocytes storage capacity. The above results in an increased plasma fatty acids concentration (dyslipidemia) with a subsequent build-up of lipids in non-adipose tissues (ectopic lipids accumulation) [7,12,13]. This seems to be fraught with consequences especially in the case of striated skeletal muscle, a tissue responsible for most (~80%) of the postprandial insulin stimulated glucose uptake [7,14]. Lee and co-workers, for instance, demonstrated that even a relatively short, 12-hr, intravenous infusion of lipids may lead to a significant elevation in their intramuscular content and subsequent deterioration in insulin sensitivity of the tissue [15].

Previous investigations revealed that especially two types of lipids, i.e. diacylglycerols (DAG) and ceramides (CER), are characterized by high potential for insulin resistance generation as described, in detail, elsewhere [7,16,17].

Briefly, both DAG and CER activate a set of intracellular proteins (i.e. protein kinase δ, ζ, θ) that in turn interfere directly with insulin signaling pathway leading to a decreased incorporation of glucose transporters (GLUT-4) into the sarcolemma [7,16,18].

In result, less blood-derived glucose enters myocytes, thus promoting hyperglycemia [7,16,18]. Interestingly, both of the aforementioned phenomena (i.e. dyslipidemia and hyperglycemia) are important contributors to the micro- and macrovascular complications of diabetes [19–21].

Microvascular complications of diabetes

Retinopathy

Diabetic retinopathy is a widespread progressive pathological condition. It originates as a consequence of microvascular disease arising in the wake of hyperglycemia and glucose-mediated endothelial injury [19].

The above-mentioned changes lead to a reduced local blood flow and leakage, thus inducing retinal neuron damage which can eventually translate into loss of vision [19]. Unsurprisingly, it is the most common cause of blindness amongst adults below 69 years of age [11].

Data obtained by Kempenet al. [22] showed that it may affect almost 50% of the US diabetics as compared with barely 4% occurrence rate observed for general population [22]. Similar results were also obtained for other populations, although they tend to vary depending on diabetes duration [21,23]. Moreover, some studies demonstrate that retinopathy may start to develop even 7 years before the diagnosis of T2DM [20].

This last notion seems to be of particular importance since some studies indicate a positive correlation between the duration of hyperglycemia and retinal damage severity [24].

Nephropathy

Nephropathy is a kidney disease characteristic for long-lasting diabetes mellitus. It is caused by the kidneys' glomeruli capillary damage as evidenced by microalbuminuria (urine protein content 30-300 mg/24 h) or proteinuria (urine protein content > 300 mg/24 h) [19,20]. It is due to long-lasting diabetes mellitus, and is a prime reason for dialysis in developed countries. Moreover, this major microvascular complication of diabetes in approximately 40–60% of the cases leads to kidney failure (end-stage renal disease) and transplantation [25].

Diabetic nephropathy also significantly increases the overall mortality of diabetic patients that may be even 6 folds greater than in age matched non-diabetics [26].

Atherosclerosis and its cardiovascular complications

Atherosclerosis is an inflammatory condition characterized by the hardening and thickening of an artery wall due to a pathological process in media intima [27].

The resultant atherosclerotic plaque builds up inside the arteries, thus clogging their lumen and impairing oxygen delivery. The above process, eventually leads to many life-threatening cardiovascular complications such as ischemia, heart attack, stroke and brain damage [27,28].

Unsurprisingly, atherosclerosis and its complications are considered to be one of the greatest contributors to the overall mortality rate amongst diabetic patients [11].

A prospective study of the UK diabetic population showed that fatal cardiovascular events, i.e. main consequence of atherosclerosis, were even 70 times more common than deaths from microvascular complications [11].

TYPE 2 DIABETES AND HEALTH COMPLICATIONS OF THE ORAL CAVITY

Numerous oral cavity disorders are associated with diabetes and obesity (Figure 1, Figure 2).

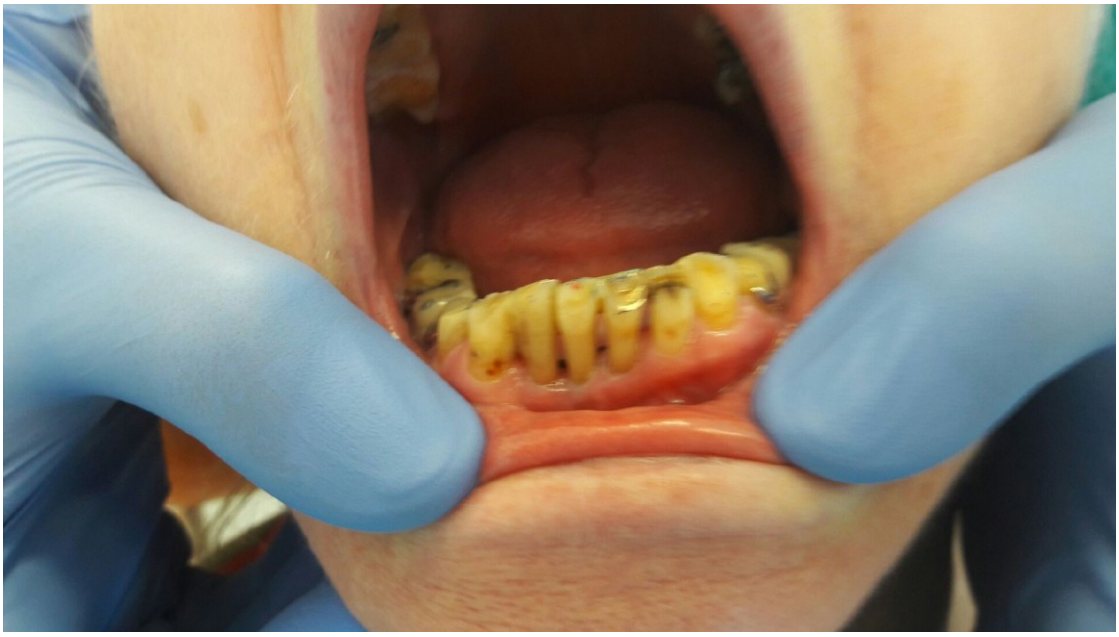

Figure 1. Gingivitis and the exposure of the lower jaw's incisors seen in a 41-old patient with diabetes

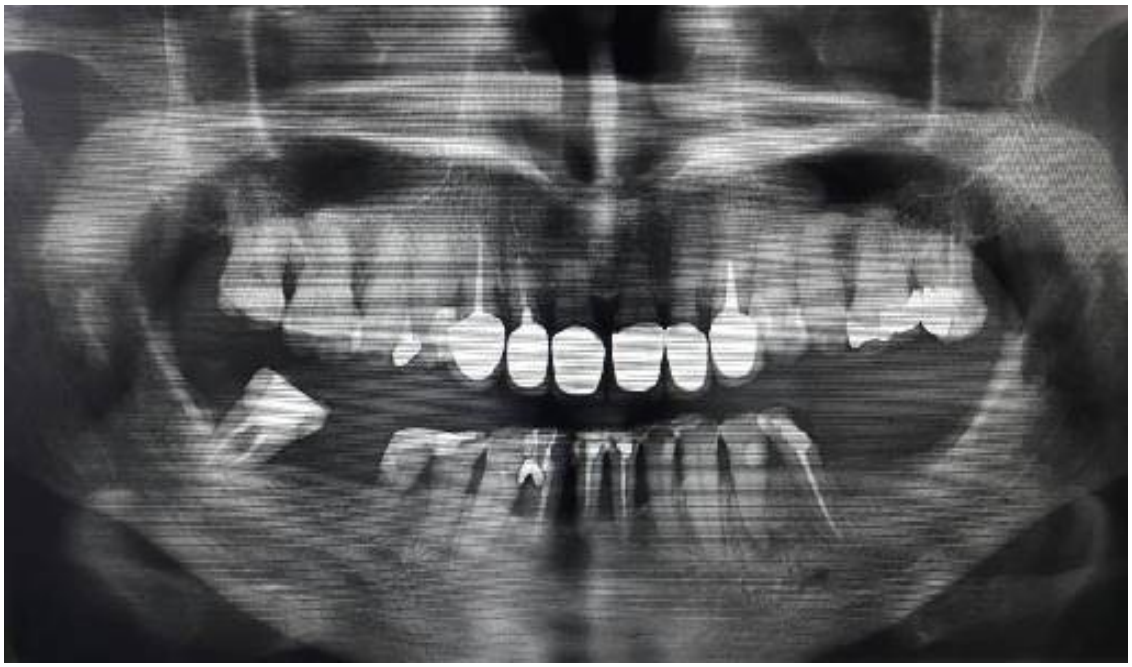

Figure 2. Pantomographic picture of a 41-year old patient with diabetes (visible bone atrophy, especially in the region of the lower jaw's incisors).

Moreover, some of them, such as periodontitis, have been identified as possible risk factors for poor metabolic control in diabetic individuals.

The most common oral manifestations of type 2 diabetes include periodontal disease, dental caries (tooth decay), salivary glands dysfunction, fungal and other types of infections, lichen planus and neurosensory disorders. Sandberg et al. [29] showed that oral cavity problems may affect even more than half of the patients with type 2 diabetes [29].

Moreover, the prevalence of oral diseases, together with increasing rates of obesity and type 2 diabetes, is growing rapidly. Thus, the aim of the current paper is to review the association between type 2 diabetes and obesity and oral health diseases.

Periodontal disease in type 2 diabetes and obesity

Periodontal disease, which is a term describing a group of diseases involving periodontium, is a well-established oral manifestation of type 2 diabetes and the evidence supporting this association are based on both animal models and epidemiological studies from human populations [30,31]. A population based study performed by Tsai et al. [32] has shown the relationship between glycemic control and periodontitis. The aforementioned authors revealed that the odds ratio for periodontitis in diabetic patients (plasma glucose level > 126 mg/dL) was almost 3 times higher (OR = 2.9) than in the control subjects [32].

Moreover, it was reduced by almost a half in the case of patients with properly controlled glycaemia (OR = 1.56) [32]. These findings correlate well with another study [30].

Lalla et al. [30], for instance, proved that among children with type 2 diabetes the odds ratio for periodontal diseases, defined as attachment loss or gingival bleeding, is 2.96 [30]. Furthermore, also meta-analysis of Taylor et al. [33], which included 48 clinical studies published after 1960, has confirmed diabetes mellitus as an important risk factor for periodontitis [33]. Interestingly, based on the results of previous studies some authors believe that periodontal diseases may well be the first clinical complication of diabetes mellitus [33].

Moreover, the relationship between long lasting poor glycemic control and periodontal manifestations of type 2 diabetes is well established and the treatment of periodontitis is an essential part of diabetes management [34,35].

Although the pathogenesis of periodontal diseases in the course of type 2 diabetes is complex, it is often believed that diabetes mellitus exaggerates inflammatory response to the oral cavity bacterial microflora [36].

However, a study of Ebersole and co-workers [36] showed that the subgingival microflora of diabetic patients did not differ as compared to that of the subjects with periodontitis but without diabetes [36].

Therefore, the exact causes are still to be determined. Other potential mechanisms explaining the relationship between type 2 diabetes and periodontal diseases include alterations in host response, collagen metabolism, vascularity and gingival crevicular fluid as well as compromised neutrophil function, decreased phagocytosis and leukotaxis [37,38].

Dental caries in type 2 diabetes and obesity

Several previously published studies revealed greater prevalence of dental caries amongst diabetic patients [39,40]. Although the occurrence of dental caries in the cases of diabetic and obese patients is higher than in healthy ones, no specific mechanisms of this phenomenon have been established, suggesting that this relationship is complex [41]. Patients with type 2 diabetes and obesity are believed to be characterized by greater exposure to cariogenic (i.e. promoting tooth decay) food, including high-caloric and carbohydrate-rich meals. [41]. Another possible explanation of an increased dental caries ratio in diabetic and obese patients is a decreased salivary flow, since it is known that diminished saliva secretion rate conveys a risk for the onset and progression of new and recurrent dental caries [41]. Moreover, the factors for caries development include poor metabolic control of diabetes and bacterial infections caused by Streptococcus mutans [42]. Data published so far indicate that even up to 25% of diabetic patients may suffer from dental caries, and another 25% experience tooth loss [43].

Salivary glands dysfunction in type 2 diabetes and obesity

The main function of the salivary glands is secretion of saliva into the oral cavity. Saliva is composed of water (99%) and enzymatic proteins (1%) and is responsible for maintenance of oral

mucosa integrity, prevention against oral infections and stimulation of appetite [44].

The secretion of saliva is mainly a result of parasympathetic stimulation. It has been demonstrated that the activation of muscarinic acetylcholine receptors (M1 and M3) in the salivary glands increases the flow rate of saliva containing low enzymatic proteins level [45]. On the contrary, stimulation of β-adrenergic receptors leads to an increased release of salivary proteins, in particular alpha-amylase [46]. Several previously published studies demonstrated, that type 2 diabetes predisposes individuals to reduced salivary flow rate [47,48]. The consequence of this salivary glands dysfunction is a condition called xerostomia (dry mouth syndrome) [49,50].

Patients with type 2 diabetes often report dry mouth syndrome, which is a result of polyuria, dehydration, and autonomic dysregulation [51]. Another mechanism of xerostomia in the course of diabetes, especially poorly controlled, is an alteration in the epithelial basement membranes of the salivary glands [52].

The prevalence of xerostomia was reported to reach 14-62% of all the cases with type 2 diabetes [43]. Although some studies provided contradictory results [53,54], still, it seems to be rather well established that type 2 diabetes as well as obesity lead to the salivary glands dysfunction expressed above all in a decreased saliva secretion [55].

A study of Chavez et al. [56] confirmed a significant reduction of unstimulated salivary flow rate in patients with poorly controlled type 2 diabetes as compared with healthy subjects [56]. In another research, Izumi et al. [47] demonstrated that type 2 diabetic patients are also characterized by a decreased stimulated salivary flow, which was accompanied by reduced enzymatic protein levels [47].

Finally, Lin et al. [48] showed that in the case of type 2 diabetes with concomitant xerostomia both salivary secretory and excretory rates are reduced [48].

Interestingly, a reduction of salivary flow rate is associated with the severity of type 2 diabetes. However, it should be noticed that some studies demonstrated no differences in the salivary glands function between type 2 diabetic patients and healthy controls (the evaluation encompassed measurement of both the unstimulated and stimulated salivary flow rate) [53,57].

Furthermore, type 2 diabetes influences saliva composition. Although a study of Piras et al. [58] found no changes in amylase expression level in the salivary glands of patients with type 2 diabetes, other reports clearly showed that the salivary glands of type 2 diabetic patients are characterized by an increased amylase activity [53,59].

Moreover, it has been proven that there is an increase in the content of salivary resistin, pro-inflammatory cytokines (IL-1b, IL-6, IL-8, and tumor necrosis factor-α) in type 2 diabetic patients [60,61].

In addition, Zalewska et al. [55] demonstrated that the salivary glands of type 2 diabetic patients are characterized by impaired morphology and function reflected in the increasing salivary N-acetyl-β-glucosaminidase and β-D-glucuronidase activities [62]. All of the above presented reports suggest that the salivary glands of type 2 diabetic patients are characterized by increased inflammation, up-regulated sympathetic activity, incremented degradation of extracellular matrix as well as impaired insulin signaling [63].

On the contrary, obesity and resulting from it insulin resistance do not affect salivary flow rate [54]. However, some of saliva compounds significantly differ between obese and healthy subjects. In a study published by Goodson et al. [64] it has been demonstrated that salivary C-reactive protein (CRP), leptin and insulin levels were increased in obese children as compared with the control ones [64]. Moreover, salivary adiponectin level in obese individuals was decreased in comparison to individuals with normal BMI [64]. As mentioned before salivary flow rate did not differ between obese and non-obese patients, suggesting that obesity did not affect salivary flow rate but the alterations of salivary biomarkers such as CRP, insulin, leptin of adiponectin could serve as indicators of metabolic disorders [64]. Another disturbance observed in the course of obesity is an increase in saliva glucose [54,57] and cortisol concentration [65,66]. Some of the pro-inflammatory cytokines isolated from saliva (i.e. tumor necrosis factor-alpha, interleukin-6, interferon γ and macrophage inflammatory protein-1 beta) were also increased in obese insulin resistant patients [67].

Moreover, an increased level of salivary oxidative stress was found in obese individuals [68]. It is worth to highlight that salivary glands dysfunctions in the case of type 2 diabetes and obesity include not only salivary glands functions expressed by saliva flow but also alterations in the structure of the glands. Some of the previously published studies revealed that chronic high fat diet feeding, a frequent cause of obesity and type 2 diabetes, contributes to lipids over-accumulation in the salivary glands [69]. It has been proven that intracellular accumulation of triacylglycerols in the

salivary glands is associated with type 2 diabetes and obesity [69]. This condition (i.e. salivary glands steatosis) is accompanied by salivary glands malfunction.

In a study of Matczuk et al. [69] it has been revealed that the increased accumulation of triacylglycerols in the salivary glands may be an important clinical manifestation of obesity and type 2 diabetes. On the other hand, phospholipids are the main components of plasmalemma and are involved in the transport processes across this biological membrane.

A study published by Kamata et al. [70] showed that diabetes leads to degeneration of acinar cells of the salivary glands and to a reduction of their secretory granules number. The above-mentioned results could have been caused by a reduction in phospholipids concentration leading to cellular membranes instability [70].

A recent study performed by Matczuk and co-workers [69] confirmed this speculations. In the aforementioned investigation the authors reported a significant reduction in phospholipids concentration in the salivary glands of obese rats with type 2 diabetes [69]. Thus, it seems conceivable that the reduction in the salivary glands phospholipids content led to the changes in the salivary glands structure and, finally, their atrophy, which in turn could be reflected in their altered functions. Moreover, recently we proved that diet induced obesity led to an inhibition of ceramide de novo synthesis together with accumulation of sphingosine-1-phosphate in the salivary glands, both of which suggest an inhibition of sphingomyelin signaling pathway in this tissue [71].

Oral infections in type 2 diabetes

Numerous microorganisms such as bacteria, viruses and fungi occur naturally in the oral cavity. In physiological conditions mechanisms of natural defense and proper oral hygiene protect oral cavity from infectious complications. It has been shown that a fungal infection in the mouth, called oral candidiasis, develops frequently among patients with type 2 diabetes [72].

Reduced salivary flow and increased glucose concentration in saliva predisposes individuals to fungal infections caused by Candida pseudohyphae [72].

The condition can manifest as white patches or ulcers on oral mucosa [72]. It is important to emphasize that oral candidiasis in not only a manifestation of diabetes but also a sign of immunocompromised state resulting from chronic or acute hyperglycemia [72].

Other infectious diseases occurring often in the oral cavity of diabetic patients are lichen planus and recurrent aphthous stomatitis. It has been established that even up to 25% of the patients with properly controlled diabetes may experience various types of oral infections, mainly candidiasis [43], whereas in the case of poorly controlled diabetes the prevalence increases to 36% [73]. Interestingly, that presence of oral infections increases the risk and severity of diabetes. This relationship is due to the spread of the inflammatory mediators via bloodstream moreover the biological pathways that intensify diabetes are the same that intensify oral diseases [34,73].

Neurosensory disorders

Neurosensory disorders are conditions resulting from diabetic neuropathy that have been reported in diabetic patients [41]. Other risk factors include reduced salivary flow, changes in nutritional habits associated with diabetes management, retinopathy, and peripheral neuropathy - a condition that severely limits diabetic patients' ability to keep the proper hygiene of oral cavity or prosthesis [41]. Taste impairment is the most common type of neurosensory disorder affecting up to 20% of diabetic patients [43].

In a study of Stolbova et al. [74] diminished taste perception has been reported in more than one-third of diabetic patients [74].

The consequence of impaired taste perception could be a disability to maintain proper diet which may well lead to poor glycemic profile observed in diabetic individuals [41].

Among other consequences of neurosensory disorders burning mouth syndrome, affecting up to 10% of individuals with diabetes, has been reported [41,43]. Another sequela of diabetes, caused by decreased strength and coordination of the cranial nerve musculature, is dysphagia [75].

CONCLUSIONS

In conclusion, diabetes is a fraught with complications disease which affects millions of people worldwide.

Many significant oral diseases were found to be related with obesity and type 2 diabetes.

Not only diabetologists, but also dentists and dental hygienists should be aware of oral

complications of diabetes, especially in a case of individuals with poorly controlled glycaemia.

The maintenance of a proper oral hygiene, strict adherence to physicians' instructions regarding diet and medications as well as regular dental examinations can help diabetic individuals in keeping oral cavity in good health.

Still, effective medical care over diabetic patients requires better understanding of pathomechanisms of its (i.e. diabetic) oral manifestations.

Thus, the oral health education should be intensively promoted among stomatologists and even more importantly amongst diabetic patients.

Acknowledgements

This work was supported by Medical University of Bialystok, grant no. N/ST/Zb/16/003/1151, N/ST/ZB17/002/3300, N/ST/Zb17/003/3300.

Conflict of interests

The authors declare no conflict of interests.

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