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INTERACTION BETWEEN DIABETES-ASSOCIATED DISORDERS OF THE SALIVARY GLANDS AND ORAL MUCOSA (literature review)

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Abstract

The aim of the study: to analyze literature sources concerning interaction between pathogenesis of lesions of the salivary glands and oral mucous membrane in patients suffering from diabetes mellitus (DM).

Conclusion. Analysis of the current literature is quite explicit on the point concerning interdependence of lesions of the salivary glands and morphofunctional changes of the oral mucosa with diabetes mellitus.

Key words: diabetes mellitus; salivary glands; oral mucosa.

Lasting hyperglycemia causing numerous lesions of the organs and tissues disturbs the functions of the salivary glands as well resulting in decreased salivation and occurrence of xerostomia [1, 2, 3-8]. The latter one due to increased exfoliation of the epithelial cells is able to provoke a number of changes in the mucous membrane of the oral cavity: speech disturbances and deterioration of taste perception [5, 9]; high susceptibility to the spread of pathogenic non-candidal microorganisms and infectious complications [6, 7, 10]; development of oral candidiasis [10]; coated tongue; unpleasant bad breath [11, 12]; periodontal diseases; demineralization of teeth and appearance of white spots [7, 13]; caries,

slow healing of wounds; fissures of the tongue [14]; development of lichen ruber planus; ulcer of the mucous membrane [15, 16]; mucous cysts, petechial hemorrhage, hyperkeratosis and atrophy of lingual papillae [5, 9]; angular cheilitis, gingival hyperplasia [7]. The most frequent disturbances are varicose dilation of the lingual veins and erythematous candidiasis [10-12]. Unfavourable consequences of saliva amount reduction are intensified due to disorders of its content: increased concentrations of mucin and glucose; changes in the productin and/or effect of many antimicrobial factors; lack of metalloprotein gustin, containing zinc and is responsible for continuous maturation of the taste buds [7, 8].

Local signs are confirmed to be closely associated with the systemic ones. Today there is not any doubt concerning interdependence of periodontitis and ischemic heart disease, effect of periodontitis produced on advancing of cardiovascular diseases in patients suffering from DM [17, 18-20]. Periodontopathic pathogens isolated from atherosclerotic plaques of the coronary arteries confirm interrelations between periodontitis and ischemic heart disease [21]. These microorganisms are considered to penetrate into the blood flow, join fatty plaques on the walls of the coronary arteries and promote clot formation. Up-regulation of cytokines and other mediators of inflammation play a key role in this process [17].

Periodontal diseases increase the risk of other systemic pathologies: infarction, stroke, respiratory diseases including pneumonias, osteoporosis and joint affection [18-22].

It is not only sugar level in the blood that causes occurrence of oral complications after diabetes and deteriorates their course, but periodontal diseases as well which make glycemia control more complicated [23, 24].

Since the amount and content of secreted saliva under conditions of diabetes are a triggering mechanism promoting occurrence of many oral complications, at first it should be reasonable to characterize morphofunctional state of the salivary glands in case of this ailment.

Insulin-dependent DM causes considerable changes in the morphology of the salivary glands, and thus – the mechanisms of salivation [25-27]. Sialosis is a frequent sign of the salivary gland pathology with diabetes. It is mainly manifested by enlargement of the parotid glands which is usually asymptomatic [25, 26, 28]. With diabetic sialosis enlargement of the volume of the parotid glands is associated with adipose infiltration of the parenchyma. These changes occur both in the acinar cells and the cells of the excretory ducts [29]. The disease with diabetes is of a degenerative character. It is associated with changes of the nervous-vegetative regulation of the glands, demilienization of the nerve fibers, and further atrophy of the myoepithelial cells. It disturbs the mechanism of saliva secretion resulting from the

stimulation of alpha and beta adrenergic receptors of the acinar cells, which physiologically causes exocytosis leading to hyposalivation and dry mouth [30].

Light optic examination and scanning electron microscopy of the parotid and submaxillary glands of mice prone to diabetes genetically (Nod) showed atrophic changes of the nuclei and cytoplasm, disorganization of biological membranes, increase of fibrillary components of the extracellular matrix, and cells in inflammatory conditions [31]. Insulin therapy produces a positive effect on restoration of these changes, but does not eliminate them completely [32, 33]. The authors consider that such destruction of the salivary glands results in changes of their functional parameters.

Certain attempts were made to determine protein biomarkers of diabetic origin xerostomia in saliva. The difference of gene expression of the parotid gland was identified on mice with xerostomia without diabetes, those suffering from obesity, and mice with diabetes with further examination of protein expression coded by these genes in the parotid gland and saliva. Chitinase expression was found to be more pronounced in the cells of the parotid acinar cells of mice with diabetes in comparison with other two groups. Therefore, increased expression of chitinase and activity of appropriate enzymes can characterize autoimmune immunity in mice, but further investigations are necessary in order to assess the use of these parameters as xerostomia biomarkers in the human body [34].

Interrelations between high occurrence of oral diseases in patients with DM and disturbance of salivation today are associated with changes of the content of certain biologically active substances in saliva. These salivary proteins are essential for maintenance of integrity of the teeth [35, 36]. Staterines, salivary proteins, participating in the formation of the enamel film and calcium hemostasis regulation play a leading role. Diabetes mellitus influences upon both salivation and secretion of proteins of the salivary glands resulting in an increased susceptibility to infections of the mucous membranes, demineralization of teeth and caries [37]. Both small and large salivary glands secrete staterines [38]. Immunohistochemical studies performed with the use of monoclonal antibodies confirmed that in the sumbaxillary, parotid and small labial glands of patients with DM expression of staterines decreases [39].

Investigation of the nature and mechanisms of development of xerostomia during recent years enabled to find a number of molecular mechanisms responsible for this phenomenon. One of these mechanisms is disorder of the intracellular localization of aquaporin-5 (AQP-5) and expression of AQP-5 protein in the salivary glands [40]. The studies conducted showed that in spite of increasing of mRNC AQP-5, the content of AQP-5 protein was low in the parotid glands of patients with DMin comparison with the control. The

authors consider that the lack of AQP-5 translocation into the salivary glands in response to muscarine agonists and inhibition of AQP-5 protein expression can lead to diabetic xerostomia.

Another possible mechanism of xerostomia can be found in disorders of SLC5A1 gene expression, which codes Na (+)-glucose contransporter SGLT1 – a protein which transports not only glucose but acts as a water canal as well [41]. Decrease of salivation caused by diabetes is associated with an increased expression of mRNC SGLT1 in the parotid and submaxillary glands. Due to this fact an increased content of SGLT1 protein in the luminal membrane of the excretory duct cells at the expense of water reabsorption can promote diabetes-associated decrease of salivation. Moreover, SGLT1 protein was reduced in the myoepithelial cells of the parotid gland of animals with diabetes, therefore salivation can be lower due to reduced contractile activity of cells. Administration of insulin during six days to rats resulted in a reverse development of all the changes. Recent investigations of certain authors showed that SGLT1 activity of the plasma membranes is regulated by the sympathetic nervous system by means of proteinkinase A [42].

Many investigations were carried out to characterize biochemical changes occurring in saliva of patients with DM. these changes refer to the concentrations of glucose, whole protein, albumin, lysozyme, peroxidase, electrolytes (sodium, potassium, chlorine, phosphorus, magnesium and calcium), amylase, IgA and buffer capacity [43-46]. Increased levels of urea and whole protein, and decreased level of microalbumin were found in saliva of patients with DM, though there were no considerable changes found in the concentration of amylase, sodium, potassium and chloride [47, 48]. Other data suggest that these results can differ in various groups of patients [49, 50].

As it has been mentioned above, usually salivation is reduced in patients with diabetes resulting in xerostomia. Meanwhile, in patients with autonomous diabetic neuropathy salivation is usually excessive, which cannot be reliably explained. Though there is a suggestion that it results from the loss of inhibitory neuron mechanisms [4, 51].

Modifications of the immune status play an important role in disturbance of functions of the salivary glands with diabetes. Due to this fact certain attempts are made to supply or change insulin therapy into immune therapy. Assessment of anti-CD3 effect of the monoclonal antibodies as alternative immune therapy in order to renew the salivary glands of spontaneous diabetic rats showed that changes of cellular architectonics, thickening of the extracellular matrix and inflammatory process in the glands of such rats considerably decrease under effect of such immunotherapy [52].

Primary lesions of the salivary glands caused by hyperglycemia become deeper due to the changes of other hormones and disturbance of their interaction with receptor cells in case of advancing diabetes [32]. Assessment of the substitution therapy effect by estrogens in combination with insulin to correct morphofunctional state of the salivary secretory cells and expression of insulin-like growth factor (IGF) of spontaneously diabetic mice found (NOD) restructuring of the gland tissue and regulation of expression of IGF-I receptors under the influence of such supplement therapy. Estrogens promote effective restoration of the salivary secretory cells, demonstrating that this hormone itself and especially in combination with insulin can be very important for reversion of tissue damage caused by hyperglycemia.

Conclusion. Analysis of the current literature is quite explicit on the point concerning interdependence of lesions of the salivary glands and morphofunctional changes of the oral mucosa with diabetes mellitus.

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