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CURRENT VIEWS ON PATHOGENESIS OF ORAL COMPLICATIONS WITH DIABETES MELLITUS (literature review)

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Abstract

The aim of the study is to analyze current views on pathogenesis of lesions of the oral mucous membrane in patients with diabetes mellitus (DM).

Conclusion. Analysis of the world scientific literature is indicative of the fact that deterioration of the blood circulation and oxidative stress underlie oral complications of DM.

Key words: diabetes mellitus; oral complications.

Morphological studies found available changes of the oral mucosa at the very early terms of DM development – duration from 1 to 5 years. The earliest structural changes of the oral mucosa are manifested by garish hyperemia of the subepithelial microscopic vessels and perivascular swelling [1]. In case of a longer course of the disease structural and functional disorders of the oral mucosa occur due to atrophic changes.

The most severe oral complication of DM is various manifestations of periodontitis from its primary stage gingivitis to periodontitis [2, 3]. Occurrence of periodontal sickness with DM ranges from 51 to 98 %. At the same time, in 10% of patients with periodontitis DM is diagnosed [4, 5].

The main role in pathogenesis of periodontal diseases in patients with DM belongs to

angiopathy [4-6]. A trigger mechanism of diabetic microangiopathy is carbohydrate metabolic disorders, as well as metabolic disorders of glycosamines which determine functional and structural integrity of the vascular basement membrane.

Changes of the periodontal vessels with DM are of a peculiar character: as a rule, their lumen is not closed completely, but the wall is always damaged [1, 5].

Microflora of the gingival slit (endotoxins and enzymes of microorganisms) causes inflammatory-destructive changes, and overload of the periodontal tissues further deteriorates their condition [7]. It should be noted that high glucose concentration in the gingival fluid of patients with DM promotes reproduction of microbes and quick formation of dental deposits [8, 9].

Microcirculatory disorders peculiar for patients with DM deteriorate when periodontitis occurs due to immune-inflammatory response which explains the mechanisms of interrelations between DM and periodontitis. In addition to deteriorated microcirculation promoting realization of these interrelations, changes of immune-inflammatory response to bacterial pathogens, decreased metabolism of the connective tissue, worse wound healing, formation of advanced glycation end products (AGE) play an important role [7, 10].

In spite of similarity of the components contained in the bacterial biofilm in the dental deposits of patients with DM and without this pathology, immune-inflammatory response to these pathogenic bacteria in patients with diabetes are modified [11]. Immune functions of neutrophils such as adhesion, hemotaxis and phagocytosis in patients with DM are disturbed [9, 12]. Moreover, hyperreaction of monocytes/macrophages to bacterial antigens is admitted, especially during episodes of hyperglycemia resulting in an increased production of pro-inflammatory cytokines IL-1β and TNF-α [13]. In addition to disorders of immune-inflammatory reactions metabolic disorders of the connective tissue are formed which are closely associated with metabolic control level [7, 8, 14]. Under effect of hyperglycemia metabolism of the osseous tissue and bone regeneration processes suffer at the expense of inhibition of cellular proliferation of osteoblasts and collagen synthesis [15-17]. Decrease of regenerative processes under conditions of hyperglycemia occurs with underlying apoptosis of fibroblasts and osteoblasts [18, 19].

Clinical and experimental observations demonstrated that hyperinflammatory reaction plays an important role in damage of the mucous membrane and destruction of the parodentium. This reaction is characterized by an increased secretion of inflammatory mediators, such as TNF-i IL-6, and systemic markers of inflammation [8]. Long hyperglycemia in patients with diabetes results in glycosylation of the structural proteins and

lipids in the extracellular matrix and connective tissue, as well as the vascular wall tissue [20]. These vascular changes cause disorders of capillary circulation and release of oxygen free forms resulting from systemic inflammatory response [21]. Moreover, monocytes and endothelial cells can interact with advanced glycation end products through their receptors (RAGE), which intensifies secretion of cytokines and inflammatory mediators by these cells, especially in response to antigenic or bacterial stimulus [22].

Bot periodontitis and DM are accompanied by systemic inflammatory reaction associated with chronic increase of inflammatory mediators including IL-1, TNF, IL-6, PGE2, C-reactive protein and fibrinogen [8, 23]. When these pathological conditions are associated, such hyperinflammatory reaction and intensification of pro-inflammatory effect of AGE / RAGE on bacterial antigens can lead to systemic inflammatory reactions and excessive expression of inflammatory mediators.

Since periodontal infections are mostly associated with gram-negative bacteria, cytokines can also be secreted by cells in response to stimulation of bacterial lipopolysaccharides. In this case cytokine production is mediated through Toll-like receptor [24, 25]. Summation of these mechanisms results in hypersecretion of TNF-α, IL-1β, IL-6 and PGE2, which are involved into destruction of the periodontal tissue and formation of periodontitis [13, 26]. Moreover, these cytokines block activity of lipoproteid lipases leading to hyperlipidemia [27]. TNF-α promotes glycogenolysis and deteriorates glucose digestion by cells intensifying hyperglycemia [27]. Acting on hepatocyte level TNF-α and IL-6 result in formation of C-reactive protein [29]. Therefore, systemic inflammatory reaction associated with DM and periodontitis of diabetic nature intensifies metabolic regulation disorders and severity of periodontal disease, and becomes a connecting link between chronic oral and systemic inflammatory diseases [2, 30].

Microcirculatory disorders in the periodontal tissues are associated with abnormal growth and regeneration of the blood vessels [31, 32]. Accumulation of AGE in the periodontal tissue of patients with DM also plays a negative role in microvascular changes [21]. Irreversible binding of AGE with collagen results in the formation of macromolecules accumulated in the basement membrane of the endothelial cells, which makes them thicker and disturbs a normal transport through the membranes essential for maintenance of hemostasis in the oral cavity [33]. Moreover, AGEs stimulate production of vascular endothelium growth factor (VEGF) – cytokine, which also participates in microvascular complications provoked by DM, and its content in the gingival tissue of patients with DM is high [34]. There are certain evidence showing that DM effect on VEGF content in the

periodontal soft tissue does not depend on metabolic control, that is, it results from “glycemic memory” [35].

Thus, there is a bilateral association and interdependence between DM and periodontal diseases. Poor control of glycemia is confirmed to be associated with more severe periodontal lesions [11, 36]. At the same time, in patients with DM and untreated periodontitis metabolic control over diabetes, as a rule, is complicated [37], and severe long inflammation in patients with periodontitis often becomes a cause of DM exacerbation. An adequate treatment of the periodontal tissue improves a metabolic state of patients [2, 38].

Today certain biomarkers of periodontal state are identified including those with DM. They can be considered as risk factors promoting occurrence or progressing of the disease [39]. The markers of periodontal tissue degradation are considered high activity of collagenase, lysosomal and cytoplasmic enzymes, and matrix metalloproteinases in the gingival fluid and saliva [40]. Assessment of collagenase activity in the gingival fluid with unsatisfactory and qualitative control over glycemia showed that collagenase activity in patients with diabetes is higher than that in healthy individuals.

Clinical examination of the role of lysosomal enzymes such as beta-glucuronidase and elastase, cytoplasmic enzymes such as lactate dehydrogenase, acting like biomarkers of periodontal destruction showed that it is beta-glucuronidase level but not lactate dehydrogenase predicts high probability of periodontal damage [95]. However, certain authors consider decreased lactate dehydrogenase level as a marker of periodontal damage as well [41].

Oxidative stress, especially decreased activity of antioxidant defense, also plays a great role in destruction of the periodontal tissue [42]. For example, in patients with type 1 and 2 DM glutathione level in saliva is lower than that in healthy individuals with periodontal diseases. In both groups of patients reduced glutathione level positively correlates with the depth of gingival pocket probing, and general antioxidant activity correlates with the state of secretion of the salivary glands [43, 44].

Antioxidant protection is known to decrease both with DM and periodontitis [45]. The results show that activity of superoxide dismutase (SOD) in the gums increases with DM and decreases with periodontitis. The authors also demonstrate relations between SOD activity in the gums, periodontal status, the content of glycosylated hemoglobin and glucose, and high density lipoproteins. Such an increase of SOD activity is considered as an adaptive mechanism.

Unfavorable effect of hyposalivation in patients with DM concerning the state of the

mucous membrane and periodontal tissue is intensified by the deficiency of antimicrobial properties of saliva under such conditions. Antimicrobial activity of saliva is provided by various proteins acting by means of different mechanisms [47]. Certain proteins (mucinous and non-mucinous glycoproteins, lysozyme) are able to agglutinate microorganisms or competitively block bacterial access for their natural places of binding on the surface of the mucous membranes of teeth [48]. Immunoglobulins of saliva (secretory IgA mainly) are recognized and specifically bound by the superficial molecules [51, 52]. Such proteins as lysozyme histatin, transferrin, lactoferrin and lactoperoxidase possess direct antimicrobial properties [53, 54]. Saliva also contains buffer systems such as sodium bicarbonate and low molecular peptides which neutralize harmful final acid products of microbial metabolism [55]. Certain proteins of saliva are able to perform functions of bacterial receptors and their metabolites, which initiate formation of biofilm – dental deposit [56]. Saliva is also a reservoir for populations of microorganisms, their metabolites and enzymes, such as proteinase and sialydase, which can cause degradation of the superficial epithelial molecules and influence on colonization of non-oral pathogens [57]. Since saliva possesses such protective functions, its deficiency in patients with DM often results in infection by pathogenic bacteria, fungi and viruses [58]. It is promoted by disorders of the microbial ecology in the pre-epithelial biofilm in the patients [59]. Normally, the mucous membrane of the oral cavity is colonized with more than 200 kinds of microorganisms, which creates a high potential for bacterial and fungal infections, and requires efforts of congenital protection mechanisms. The oral cavity contains at least four microbial ecological niches with a certain degree of changeability in the content of local flora: saliva, tongue, subgingival and supragingival dental deposit [56]. Different agents of Streptococcus species are prevailing flora of saliva, tongue andsupragingival deposits [60]. These synanthropic bacteria are able to modulate colonization of yeasts competing for nutrients and adhesion places [61]. Investigation in vivo and in vitro confirmed Streptococci can prevent oral colonization by Candida [62].

Disorders of these interrelations under conditions of DM result in excessive development of pathogenic microorganisms in the pre-epithelial biofilm of the oral mucosa. In particular, DM refers to risk factors promoting oral candidiasis, which is the most common opportunistic fungal infection among patients with diabetes [63, 64]. It is associated with an increased glucose level in saliva, decreased salivation and reduced activity of neutrophils concerning Candida [2, 65], as well as changes in the content of saliva at the expense of decreased content of lactoferrin, lysozyme and lactoperoxidase [66, 67].

Other oral complications are associated with candidosis in patients with DM: prosthesis-induced stomatitis, angular cheilitis and middle rhomboid glossitis, disorders of taste perception, which have mixed bacterial and fungal etiology [63, 66, 67].

Susceptibility to oral infections in patients with DM is known to result in caries and loss of teeth [68, 69]. Dysfunctions of the salivary glands, periodontal tissue and sensory disorders can increase probability of development of new cases and relapses of caries and loss of teeth.

Conclusion. Analysis of the world scientific literature is indicative of the fact that deterioration of the blood circulation and oxidative stress underlie oral complications of DM.

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