Review

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Certain aspects of the systemic etiopathogenesis of dystrophic-inflammatory periodontal diseases (a literature review)

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of the article

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Aim. To study the main pathogenetic mechanisms in the development of dystrophic-inflammatory periodontal diseases by analyzing scientific research results covered in current specialized literature.

Material and methods. Searching, systematization, processing and analysis of scientific sources, which present modern theories of pathogenesis and development of dystrophic-inflammatory periodontal diseases.

Results. The conducted data analysis from modern literary sources proves that the progression of dystrophic-inflammatory periodontal diseases depends not only on the development of local inflammation in the periodontal tissues caused by the dental plaque microflora, but also it is a reaction to the influence of systemic factors. They lead to profound changes in the body internal environment and, as a result, to structural damage of the periodontal tissues. At the same time, the results obtained do not allow the authors to clearly assess the nature of these relationships and require further in-depth studies.

Conclusions. Understanding the pathogenetic mechanism of periodontal diseases allow developing optimal measures for their diagnosis, prevention and treatment.

Деякі аспекти системного етіопатогенезу дистрофічно-запальних захворювань пародонта (огляд літератури)

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Ключові слова: захворювання пародонта, патогенез, генералізований пародонтит, мікроциркуляція, пероксидне окиснення ліпідів, антиоксидантний захист, імунологічні зміни.

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Мета роботи – вивчення основних патогенетичних механізмів розвитку дистрофічно-запальних захворювань пародонта шляхом аналізу результатів наукових досліджень, що наведені в сучасній фаховій літературі.

Матеріали і методи. Здійснили пошук, систематизацію, опрацювання й аналіз наукових джерел, в яких наведено сучасні теорії патогенезу та розвитку дистрофічно-запальних захворювань пародонта.

Результати. Аналіз відомостей сучасної наукової літератури доводить, що прогресування дистрофічно-запальних захворювань пародонта залежить не тільки від розвитку локального запалення, що спричинене мікрофлорою зубної бляшки, в його тканинах, але є реакцією на вплив системних факторів. Вони призводять до істотних змін внутрішнього середовища організму та, як наслідок, до структурного ураження тканин пародонта. Втім, результати досліджень не дають підстав однозначно оцінити характер цих зв'язків і обґрунтовують необхідність продовжувати роботу у цьому напрямі.

Висновки. Розуміння механізмів патогенезу захворювань пародонта дає можливість розробити оптимальні заходи з їх діагностики, профілактики та лікування.

Numerous studies and observations of recent decades have convincingly shown that chronic periodontal dystrophic-inflammatory diseases belong to the group of multifactorial diseases. An important role in their development is played by impairments in the immune system and metabolism, genetic predisposition, functional disorders of certain organs and systems, and other factors [1,2,3,4].

Aim

To study of the main pathogenetic mechanisms in the development of dystrophic-inflammatory periodontal diseases by analyzing the results of scientific research, covered in current specialized literature.

Insights into the mechanisms of the occurrence and progression of generalized periodontitis (GP) has advanced greatly over the past decades. Influential factors include violations of microcirculation and transcapillary exchange, the imbalance between immunocompetent systems, the involvement of autoimmunity, and insufficient antioxidant protection [4,5,6,7].

Chronic dystrophic-inflammatory processes in the oral cavity are manifested not only by inflammation of periodontal tissues caused by pathogenic microorganisms, but also by a complex combined imbalance between protective mechanisms in the whole body: immune and endocrine, microcirculation, neurohumoral regulation, mineral metabolism, vitamin deficiency, changes in the connective tissue metabolism, psychosomatic disorders, endotoxicosis. All these leads to a weakened body resistance, and in combination with external factors (dental plaque microbial colonization) – to the GP development [4,6,8].

In the development of periodontal dystrophic-inflammatory diseases, the combined action of three pathogenetic factors has an important role to play: microorganisms, endogenous factors, and exogenous environmental influences. The oral cavity microflora is considered as one of the most important specific stimulants of triggering mucosal

immune response. Strengthened or weakened pathological effects of a pathogen on the periodontal tissues depends on the state of immunity, which regulates the balance between microbiocenosis and the oral mucosa tissues, in particular, through cytotoxic immune response [4,5,7].

One of the determining pathogenetic factors in the development of dystrophic-inflammatory periodontal diseases is violated regional hemodynamics and microcirculation in the gingival tissue. Blood circulation in the periodontal tissues is 3–5 times more intense than in other organs. Periodontal microvessels not only provide the trophic and oxygenizing function, but also constitute its hydraulic apparatus, taking an active role in the biomechanics of the maxillofacial segment. Microcirculation disorders are often a diagnostic sign of early trophic disorders in the oral mucosa tissues. Long-term damage to the endothelium of the vascular wall plays a key role in the pathogenesis of not only generalized diseases of the periodontal tissues, but also a number of systemic diseases [1,5,8].

Scientific studies have defined that a spastic state of arterioles occurred within the gingiva with the development of periodontitis, the number of functioning capillaries decreased, intravascular blood aggregation developed and blood circulation was disturbed. Changes in microcirculation occur already in the early stages of periodontitis development and determine the pathological process progression. Perivascular abnormalities are manifested by changes in connective tissue cells, degranulation of mast cells, transformation of histiocytes into macrophages; biochemical and physical-mechanical changes in the main substance surrounding microvessels. These changes, as a rule, do not arise in isolation, but form an integral part of the inflammatory process complex development, often caused by exogenous factors, including occupational hazards [4,9].

Damage to the vascular wall during periodontal inflammation causes the activation of intravascular adhesion and platelet aggregation, results in local blood coagulation with the possible development of disseminated intravascular coagulation syndrome. Hemostasis system disorders worsen the severity of inflammatory processes in the periodontal tissues. The main factors that change the capillary wall permeability are decreased PO_2, increased PCO_2 levels, acidosis development due to the accumulation of underoxidized metabolic products (lactic, pyruvic acid, etc.), as well as such powerful factors of permeability regulation as histamine, serotonin, bradykinin, prostaglandins, lysosomal enzymes, and others. The involvement of inflammation induced by a microbial factor aggravates and accelerates destructive processes in the periodontal tissues [1,4,9].

In the pathogenesis of dystrophic-inflammatory diseases of the periodontium, disordered lipid peroxidation plays an important part. Patients with GP have increased peroxidation processes in saliva and periodontal tissues. Conjugated dienes, trienes and malondialdehyde accumulate, the levels of which correlate with the severity and course of GP. The amount of peroxide oxidation substrates, arachidonic acid, thromboxanes and leukotrienes, increases. These toxic products cause periodontal tissue hypoxia, lead to metabolic changes and dystrophic disorders [10,11,12].

Excessive production of active oxygen species causes hypoxia of the periodontal tissues, leading to activation of free radical oxidation processes. The generation of active oxygen species in tissues normally induces protective mechanisms – antioxidant and other defensive systems. In an imbalance in the ROS/antioxidant protection system with the prevalence of the former, the level of lipid peroxidation in cell membranes increases with their destruction, breakdown and release of endogenous toxins. Cell division is also impaired and unreactive products of lipid and protein peroxidic denaturation are accumulated. Activation of free radical oxidation in periodontal structures is one of the factors that inhibits its resistance to adverse effects, that sets the stage for unimpeded extension of the inflammatory process [13,14,15].

There is a specific system of antioxidant protection (AOP) in the human body to mitigate processes of lipid and protein peroxidation. The leading place in it is occupied by the intracellular enzyme catalase. The main enzymes of AOP traditionally include, in addition to catalase, superoxide dismutase (SOD), haloperoxidase, glutathione-S-transferase, glutathione reductase, ceruloplasmin, transferrin, and peroxiredoxins. The non-enzymatic link of AOP is represented by a number of low-molecular compounds, the most important among these are glutathione, vitamins E, C, A. Many researchers have demonstrated a decrease in the activity of catalase, SOD, transferrin and the central nervous system overactivity in patients with both initial forms of GP and severe stages of the GP development, especially in case of the disease exacerbation [16,17,18].

The development of dystrophic-inflammatory diseases of the periodontium is also related to an imbalance between biosynthesis and catabolism of the connective tissue intracellular component, especially non-collagen periodontal proteins. In chronic GP with the decreased activity of SOD, catalase, haloperoxidase, and cytochrome oxidase, the level of sulfhydryl groups in the gingiva increases, indicating protein breakdown [19,20]. There is a sharp decrease in the overall antioxidant activity of saliva, i.e. enzymatic systems of antioxidant protection, that causes the development of antioxidant "starvation" in the periodontal tissues. Because of increased processes of lipid peroxidation in the periodontal tissues, there is a decrease in lipoproteins, phospholipids, and triglycerides in dystrophic-inflammatory periodontal diseases. As a result, patients develop significant disorders of protein metabolism, manifested by hypo-, dysproteinemia, and hypoalbuminemia, which are due to insufficient synthesis of individual proteins in the zone of slow and fast posttransferrins, as well as a decrease in the concentration of anti-inflammatory proteins of the acute phase. This leads to a stress on the entire system of antioxidant protection, which is evidenced by elevated levels of ceruloplasmin and transferrin in the blood of patients. In the midst of this, immune system dysfunction easily occurs [12].

The course of dystrophic-inflammatory periodontal diseases is accompanied by a cascade of immunological alterations in the body of patients. During the progression of dystrophic-inflammatory processes, the spectrum of antibodies to various types of microorganisms and pathologically changed periodontal tissues increases. At the same time, local factors of antimicrobial protection, for example, salivary lysozyme, are greatly reduced. Scientific studies have proven that the interlink between the direct pathogenic action of microorganisms and the immunopathological reaction to the periodontium determines the degree and

character of the damage. In this regard, some researchers note that the pathological process course in the periodontal tissues is driven more by the body immune response than by the microflora pathogenicity [2,5].

More than 530 species and subspecies of microorganisms have been detected in biofilm samples of the oral cavity, but at the moment, not all the periodontopathogens have been identified. It is believed that at the initial stages of periodontal inflammation, microbes act as chemotoxic agents that promote neutrophil, lymphocyte, and monocyte migration to the site of microbial invasion. These cells, under the influence of microbial products, release inflammatory mediators into the environment, causing a reaction of the microcirculatory bed, which is manifested by the dilation and increased permeability of blood vessels. Morphological studies have revealed an increase of the number of neutrophils and lymphocytes in the gingival fluid and exudate, the presence of lymphocytes within the epithelial layer [20,21]. An inflammatory process in chronic obstructive pulmonary disease has also been found to be accompanied by a significant production of interleukin 1 (IL-1). But dental plaque accumulation is accompanied by antibody synthesis to bacterial components and immune complexes formation causing complement activation. Moreover, after 4–7 days, a lymphoplasmacytic infiltrate is formed in the periodontal tissues, which produces mediators to induce the proliferation of lymphocytes. The proliferative response of lymphocytes translates into infiltration predominantly of plasma cells and macrophages. Further formation of a pathological pocket, destruction of the alveolar bone process and the tooth attachment apparatus is observed [1,17].

The development of dystrophic-inflammatory diseases of the periodontium leads to a significant immune restructuring of its tissues. In patients, antibodies are detected not only to the microorganisms of periodontal pockets, but also to their own pathologically changed tissues. An important place is given to periodontopathogenic bacteria that induce an increase in the level of pro-inflammatory cytokines with subsequent destruction of the periodontal tissues. Most often, these are *Porphyromonas gingivalis, Prevotella intermedia, Aggregatibacter actinomycetemcomitans*. An association between dental plaque (biofilm) effect and the host immune response is important for the realization of bacterial pathogenicity. It depends on the number and virulence of periodontopathogenic microorganisms, resistance factors of patients, their immune status, etc. Inflammatory reactions are initiated in tissues, the cells of which secrete pro-inflammatory mediators, including prostaglandin E (PGEi), IL-1, IL-6, matrix metalloproteinases, cytokines [22].

When studying local immunity, an increase in the concentration of lysozyme, β-lysines, secretory IgA (sIgA), serum IgA and IgG, total protein has been revealed in oral and gingival fluids at the initial phases and at the 1st stage of GP development. And as the severity and intensity of destructive-inflammatory changes in the periodontium increase, the levels of lysozyme and sIgA decrease [20]. Adaptative mechanisms break down at severe degrees of the disease, manifesting in the form of an inadequate regulation of macrophage and lymphocyte number, a decrease in the functional properties of neutrophils, inhibition of IgA and sIgA secretion processes at the local level, and a violation of mechanisms for mobilizing IgG from the bloodstream [23]. In patients with GP, the content of epithelial cells and leukocytes in oral and gingival fluids increases three times compared to those in healthy people with a large percentage of immature epithelial cells [16].

Modern studies have proven the role of cytokines in the mechanisms of chronic inflammatory process development in the periodontal tissues along with other concepts of pathogenesis ("theory of bacterial plaque", "theory of tissue trophic disturbance"), that became common as the "cytokine concept". According to it, cytokines play a leading role in the development of chronic inflammatory processes in the periodontal tissues [24,25]. Proinflammatory cytokines not only adversely affect periodontal tissues, but also cause further activation of cytokine-producing cells, inhibit tissue repair and activate osteoclasts, leading to increased alveolar bone resorption [5,26,27].

Examinations of interleukin levels (IL-2, IL-6, IL-8) in GP patients with different clinical course (conditionally "favorable" and conditionally "unfavorable"), as well as TNF-α, IFN-γ, IL-12 and IL-4, have revealed a direct correlation between their levels and both clinical (inflammatory reaction activity in the periodontal tissues) and laboratory parameters in blood serum and oral fluid [9]. An increased IL-18 levels have been detected in the oral fluid of GP patients only during exacerbation, which may indicate the activation of monocytes / macrophages and dendritic cells, as their main source, in response to microbial aggression. The absence of anti-inflammatory IL-10 leads to elevated cellular bone resorption and reduced bone tissue formation [26].

Recent studies on the pathogenesis of periodontal diseases point to a number of changes in the body metabolic status, in particular, protein and carbohydrate metabolism [1,5,13,16]. Carbohydrates are involved in metabolic processes in the oral cavity, where the conditions for their assimilation by the microflora are almost ideal: constant temperature (~37 °C), moisture, close to the neutral pH value. Oral sucrose influences the composition of oral fluid and oral cavity metabolism. After eating simple carbohydrates, a peculiar burst of metabolic processes occurs due to microflora and dental plaque. Microorganisms very actively use carbohydrates for their needs and accumulate them as a reserve in the form of polysaccharide dextrans. Activation of glycolysis causes the accumulation of lactic, pyruvic and other acids in the oral cavity, the amount of which increases 9–16 times in the next 20 minutes after consuming carbohydrates, returning to the baseline level by 60–90 minutes, which causes acidification of the oral fluid.

Pyruvic acid (pyruvate) is one of the central intermediate metabolites of carbohydrate metabolism, formed in the process of glucose oxidation and glycogen breakdown in tissues, during lactic acid oxidation, and also as a result of the transformation of some amino acids. The content of pyruvic acid in human biological fluids is high, as it is involved in both carbohydrate and protein metabolism. Lactic acid, which is also a product of carbohydrate metabolism, is formed in the body as a result of pyruvic acid reduction as well as is the end product of glycolysis and glycogenolysis in anaerobic conditions. An increase in its concentration is observed in hypoxic conditions of the human body, including cardiovascular and respiratory diseases, blood loss, severe anemia, liver damage, acute purulent damage to tissues,

renal failure, malignant neoplasms, diabetes, significant physical exertion and convulsions, tetanus [27].

The enzyme lactate dehydrogenase (LDH) is a cytosolic enzyme found in all cells of the body, mainly in skeletal muscles, liver, skin, mucous membranes, as well as cells of some malignant tumors. In gingival biopsies from GP patients, the activity of some glycolytic and respiratory enzymes was studied, demonstrating the prevalence of tissue respiratory enzymes over glycolytic ones in clinically healthy periodontal tissues, and in the case of GP, prevailing glycolytic enzymes reduced the activity and disrupted the barrier function of gingival epithelial cells, resulting in epithelial attachment violation and the development of periodontal pockets. Glycogen accumulation of in the periodontal tissues indicates abnormalities in glucose metabolism due to chronic inflammation. Metabolic acidosis and a decreased pH are responsible for a decrease in the intensity of carbohydrate oxidation. An increased LDH activity in the oral fluid and neutrophil granulocytes is explained by the fact that its main source is oral microorganisms, the number of which is increased in GP patients [17,28].

An increased LDH activity in the oral fluid may indicate the activation of anaerobic carbohydrate metabolism in periodontal tissue inflammation, the products of which (particularly the lactate) cause microcirculatory disorders with an increased permeability of periodontal vessels for high molecular weight substances. It has been proven that an increase in LGH activity inevitably led to acid-base imbalances, causing a decreased pH of the intracellular environment, and directly affecting other enzyme activities. An increased LDH activity indicates preconditions for an imbalance of carbohydrate metabolism at the cellular level in GP. Therefore, with periodontal dystrophic-inflammatory diseases, certain parameters of carbohydrate metabolism are changed, since hypoxia always develops in this disease, and it is known that any form of hypoxia leads to an increased levels of lactic acid [29].

Conclusions

1. Despite a considerable number of works focused on the study on the pathogenesis of periodontal diseases, mechanisms promoting the development of dystrophic-inflammatory changes in the periodontal tissues have not been fully studied.

2. The analysis of literary sources allows us to conclude that the progression of these processes depends not only on the development of local periodontal inflammation caused by the dental plaque microflora, but also it is a reaction to the influence of systemic factors that lead to profound changes in the body internal environment and, as a result, to structural damage of the periodontal tissues.

3. The results obtained do not allow the authors to clearly assess the nature of these relationships and require further in-depth studies. More detailed analyses of the pathogenetic mechanisms will allow developing optimal complex treatment and providing effective prevention of dystrophic-inflammatory periodontal diseases.

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