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MODELING OF CHRONIC GENERALIZED PERIODONTITIS IN LABORATORY ANIMALS (LITERATURE REVIEW)

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Ключові слова: *хронічний генералізований пародонтит, моделювання, регенеративна стоматологія, лабораторні тварини*
Ключевые слова: *хронический генерализованный пародонтит, моделирование, регенеративная стоматология, лабораторные животные*

Abstract. Modeling of chronic generalized periodontitis in laboratory animals (literature review). Kopchak O.V., Marchenko N.S., Yanishevska Ya.V. *Modern experiments in the study of periodontal deseas are aimed at improving the effectiveness of innovative methods of early diagnosis, treatment and prevention of this disease in patients. The conducted analysis of the literature showed that the disorder of microcirculation occupies one of the leading places in the pathogenesis of periodontitis. Disruption of the microcirculatory bed, based on the dyscirculatory changes of the capillary blood flow is accompanied by a decrease in the intensity of blood filling of vessels, their spasm. These changes, in case of chronization, include tissue disorders of the ischemic nature, up to the development of a capillary stasis. This can lead to disorder in gas exchange, trophism and pathomorphological damage to periodontal tissues. This type of change is most typical for age-related, traumatic, vascular, and stress-induced models. Morphological lesions in the vessels, namely ischemic phenomena were most pronounced in them. Microscopically, this was manifested in the heterogeneity of the epithelial layer, the thickening of individual layers, the detachment of the epithelial lining of the mucosa. As for the basal layer, the most common was the vacuolization of cells, the appearance of a significant number of cells that lacked nuclei (pathology, indicating a decrease in functional activity, impaired regenerative properties of the cell), expansion of intercellular contacts, a sign of tissue edema. In the basal membrane (function - dissociation of the epithelium from the actual lining of the mucous membrane), collagen fibers were loose, hypertrophic, their hyperplasia was observed, neutrophil leukocytes, lymphocytes, histocytes were found between the fibers, this testified to changes in cells. Some models lack a clinical picture of chronic hyperplastic periodontitis. The disorders consisted of changes in normal metabolism in periodontal tissues, decreased immune function, changes in morphological structure without induction of the inflammatory process.*

Реферат. Моделювання хронічного генералізованого пародонтиту в лабораторних тварин (огляд літератури). Копчак О.В., Марченко Н.С., Янішевська Я.В. *Сучасні експерименти в дослідженні захворювань пародонту спрямовані на підвищення ефективності інноваційних методів ранньої діагностики, лікування та профілактики цього захворювання в пацієнтів. Проведений аналіз літератури показав, що розлад мікроциркуляції посідає одне з провідних місць у патогенезі пародонтиту. Порушення мікроциркуляторного русла, що базується на дисциркуляторних змінах капілярного кровотоку, супроводжується зниженням інтенсивності кровонаповнення судин, їх спазмом. Ці зміни у випадку хронізації призводять до тканинних порушень ішемічного характеру, аж до розвитку капіляного стазу. Це може призвести до порушення газообміну, трофіки та патоморфологічного ураження тканин пародонта. Такий характер змін найбільш типовий для вікової, травматичної, судинної та стрес-індукованої моделей. Морфологічне ураження в судинах, а саме ішемічні явища, були найбільш виражені саме в них. Мікроскопічно це проявлялося в неоднорідності епітеліального пласту, потовщенні окремих шарів, відшаруванні епітеліального покрову слизової оболонки. Що стосувалося базального шару, то найпоширеніше виявилась вакуолізація клітин, поява значної кількості клітин, у яких були відсутні ядерця (патологія, що вказує на зменшення функціональної активності, порушення регенеративних властивостей клітини), розширення між-клітинних контактів, ознака набряку тканин. У базальній мембрані (функція – відмежовування епітелію від власне пластинки слизової оболонки) колагенові волокна були рихлі, гіпертрофічні, спостерігалась їх гіперплазія, між волокнами виявляли нейтрофільні лейкоцити, лімфоцити, гістоцити, що свідчили про зміни клітинного імунітету. У деяких моделей відсутня клінічна картина хронічного генералізованого пародонтиту. Порушення полягали в змінах нормального обміну в тканинах пародонта, зменшенні імунної функції, змінах морфологічної структури без індукції запального процесу.*

According to WHO, periodontal disease is an important socio-economic problem, and periodontitis remains the main cause of tooth loss in the adult population. Unchanged periodontium is diagnosed in only 2–10% of people, while the prevalence of inflammatory periodontal disease ranges from 40–60 to 94.3% in individuals of different age groups [7]. Current methods of treating periodontal tissue disorders include the pathogenesis of periodontal disease, using non surgical or surgical techniques [22, 25, 36, 38], periodontal tissue regeneration [13], tissue engineering and growth factors [20, 30] (stem cells, autofibroblasts, blood plasma autocryolysis, PRP therapy, hialyrinic acid), which require sufficient study.

Scientists working in various fields of medicine emphasize the importance of the prevention and treatment of periodontal diseases as an integral part of modern preventive medicine and reduce the negative impact of this disease on the overall health [15].

The main pathogenic factors in the development of chronic generalized periodontitis are old age, stress, misuse of drugs, hormonal changes. These factors and scientifically gounded results of clinical trials results can be used to experimentally reproduce chronic generalized periodontitis in laboratory animals. Their purpose is to observe the development of pathology in time, to study the pathogenesis and features of the treatment of relevant pathological processes in the experiment. Carrying out research on laboratory animals also gives the opportunity to gain new knowledge in the field of biomedical sciences, in the field of therapeutic dentistry including.

The purpose of the work it is review of scientific works concerning the main models of development of periodontitis in laboratory animals. The data obtained during preclinical studies of chronic generalized periodontitis (CGP) and for in-depth study of the effectiveness of regenerative and non surgical therapies have been used.

MATERIALS AND METHODS OF RESEARCH

Literature search has been conducted among the library sources, searching systems PubMed, Google Scholar, CyberLeninka, as well as electronic archives of domestic and foreign medical publications.

RESULTS AND DISCUSSION

Some species of laboratory animals are most commonly used in the animal world: rodents, rabbits, dogs and primates [34]. Existing animal models of periodontitis provide a wide range of results, which makes it possible to investigate the pathogenesis of diseases, to study the development and sequence of histological changes in tissues and organs of the oral cavity, to carry out different, including both traditional and innovative treatment options for chronic generalized periodontitis [14, 37].

According to the law of Ukraine on approval of the procedure for conducting scientific experiments, experiments on animals [3], adhering to all the conditions specified in the European Convention for the Protection of Vertebrate Animals used for research and other scientific purposes of 18.03.1986 [1], for experimental studies rats are the most suitable [23]. Experimental research adheres to the "Common Ethical Principles of Animal Experimentation", approved by the First National Congress on Bioethics (Kyiv, 2001), Directive 2010/63/ EU of the European Parliament and Council on the protection of animals used for scientific purposes [27, 33]. The experiments on rats are especially facilitated by the small size of the animals, the age of the selected individuals, the genetic study of the lines of the animals, and the economic benefits of conducting studies on small laboratory animals [21]. It should be emphasized that, at the same time, anatomical and structural features of periodontal tissues and the development of pathological inflammatory diseases in rodents are significantly different from the analogs in the other mammals, pathogen bacteria in their oral cavity (e.g. *F. nucleatum, P. heparinolytica, Prevotella spp., P. micros*) are associated with the development of inflammatory periodontal diseases in humans [39].

Consider in detail the most used models of chronic periodontitis in experimental dentistry, their positive sides and negative features of their course.

Stress-induced periodontitis. In the work of L.H. Duryagina a stress-induced model of chronic periodontitis is described. Morphometric and histological examination of the degree of alveolar process dystrophy in experimental animals was conducted in the course of the study. The purpose of the work was to study the prevention of generalized periodontitis development in chronic neuro-emotional stress. Laboratory adult rats, divided into the following groups were used as the object of study: 1 group – control (intact), 2 – group of animals with model of generalized periodontitis, 3 – group of animals with simultaneous modeling of generalized periodontitis and chronic stress, 4,5 groups – in animals against modeling of generalized periodontitis and the effects of chronic stress, appropriate variants of disease prevention were carried out according to the method developed by the authors. The most similar model to human chronic periodontitis was found in 3d group of animals. Hyperemia of the mucous membrane of the gums with cyanotic tinge, enlargement of the interdental papillae and marginal part of the gums, destruction of the annular ligament of teeth,

presence of deep periodontal pockets filled with serous purulent exudate, dental mobility was observed. Hypertrophy of collagen fibers, signs of connective tissue edema were revealed as well. This variant of model of generalized periodontitis developed on the background of chronic stress reaction [5].

An additional evaluation of the dystrophic process in the periodontal tissues of experimental animals by the biometry method showed its high intensity in the alveolar process area namely in combined modeling of generalized periodontitis and chronic stress [11]. Also, chronic stress significantly increased bone loss resulting from ligature-induced periodontitis by a local increase in proinflammatory and proresorptive factors [12]. At the same time, these and other authors show that the inflammatory processes in this model of pathology are not presented clearly enough and in relief [9].

Vascular model of chronic periodontitis, reproduced on the background of lesion of the capillaries (due to diabetes). Diabetes mellitus contributes to the development of infectious diseases in patients, including oral cavity. New data demonstrating the important pathogenetic role of the microbial factor in the development of vascular complications of diabetes appeared. In this regard, in the experiment this approach was developed and used for reproduction in laboratory animals of an appropriate pathology model [10]. Rats were administered alloxan (intraperitoneally, 100 mg / kg once). On the 7th day of the study in rats, an increase in serum activity of indicators of malondialdehyde and elastase was detected. These indices are signs of inflammation, and the rates of lysozyme and catalase were almost 2 times below normal. The authors substantiated the feasibility of their approach also by the fact that in diabetes vessels are damaged first, in the latter disorders of the processes of microcirculation are observed, this causes the development of further complications, extremely important for the progression of chronic generalized periodontitis both in animals and in patients.

Thus, it was found that there is a relationship between the development of diabetes and a decrease in local immunity, increased oxidation processes in the mucous membranes of the oral cavity and increased exposure to activated pathogens, agents.

Model of chronic periodontitis induced against immunosuppression. It is proved that immune diseases occur chronically, with periods of remission alternating with exacerbations. The results of these studies relate to the known side effects of long-term antibiotic administration. In addition to hepatotoxic and allergic effects, the development of oral dysbiosis (dysbacteriosis) plays a significant role in the effects of antibiotic therapy. This is explained not only by the ability of most antibiotics to inhibit the growth of probiotic microflora, but also by their destructive, altering effect on tissues and biopolymers in various tissues of the periodontium, which leads to the loss of their barrier physiological functions.

Defining in rats' gums enzymatic activity of a specific protein-lysozyme, as one of the factors of nonspecific immunity, it was determined that even small doses of lincomycin caused a dose-dependent decrease in lysozyme content in the gum tissues of animals. The data obtained by the authors indicate a negative impact of antibiotic therapy on periodontium, which is accompanied not only by the activation of proteolysis, but also by decrease in nonspecific immunity. These changes determine the quantitative increase in periodontal pathogenic bacteria and chronization of the inflammatory process in the gums and other tissues of experimental animals against the background of antibiotic-induced activation of proteolytic activity in the gums. The decrease in lysozyme activity in the gums is followed by further microbial lesions and the development of pathology of the corresponding oral tissues.

Age-related model of periodontitis is extremely important and is described in detail in the works of R.S. Turchin, V.P. Pyuryk, and G.B. Prots. These and other authors substantiate their choice by the fact that many domestic and foreign scientific works provide data on the prevalence, features of the course and treatment of chronic generalized periodontitis in the elderly. It was previously thought that scientific research on age animals was disadvantageous, and the model was time-consuming and labor-intensive.

Treatment of elderly people with chronic generalized periodontitis has significant difficulties and is considered ineffective by its results [26]. The decisive etiological association of periodontitis in geriatric group of individuals is considered to be microbial agents as trigger factors of this pathological process. When the process of inflammation spreads to the deep parts of the periodontium, vascular system and periodontal ligament additionally become the object of the lesion. There are also a number of pathophysiological changes that lead to dysfunction of the microcirculatory channel of the oral tissues and the development of local ischemia of periodontal tissues. An unbiased analysis and discussion of these results testifies to the relevance and importance of the development and use of an age-related model of chronic generalized periodontitis in experimental conditions. This is due to the initial progression of disorders in periodontal tissues, chronization of the process and age-related changes,

predominance of degenerative phenomena over regenerative compensatory reactions.

Infection-inflammatory model. When studying the pathogenetic features of periodontitis, the basic requirement for any model is that it objectively reproduces both the local disorders observed in the foci of periodontal inflammation and is suitable for the investigation of systemic disorders. This applies to the activation of peroxide processes, immune disorders, necrotic and cytokine reactions, which largely depend on the nature of the pathology and its consequences [26].

The usage of carrageenan experiments with a mixture of pathogens provides reproduction of a rapid method of modeling acute infectious periodontitis in animals, reflects some pathogenetic links of the inflammatory process and approaches the clinical manifestations in patients [8]. At the same time, the obtained experimental model can be used to evaluate disorders only in inflammatory periodontal diseases and to develop new methods and treatments. The proposed method provides the reproduction of an experimental model of acute periodontitis, but can not be used in experimental practice to study the etiopathogenesis, course and features of experimental therapy of chronic generalized periodontitis in experimental animals.

The traumatic model of chronic periodontitis is considered to be the perfect and most widely recognized model of chronic generalized periodontitis. The traumatic model is caused by the action of a chronic external factor on the periodontal tissue. The latter causes mechanical damage to the gums. This, for example, is observed in the experimental conditions when the appropriate ligatures are applied to the tooth (teeth) neck, that is, when creating occlusion [28]. This model is called induced periodontitis. Experiment on the study of this plane as well was conducted and described in many papers. The method of modeling an experimental local periodontal is the purpose of studying the effectiveness of autologous multipotent mesenchymal stromal cells, being one of them [4].

Modeling of traumatic form of chronic periodontitis was reproduced in experimental animals by fixing the ligature around the tooth neck [2]. Observations showed that in the first week after application of the metal ligature, hyperemia and edema of the gum line appeared on the tooth neck, and the interdental papillae quickly lost their anatomical shape. In the second week from the beginning of the experiment periodontal pockets appeared, the mobility of the teeth first appeared, or was determined. The marginal gums of the experimental animals acquired a roller-like appearance, tooth retraction was observed, interdental papillae separated from the tooth neck became bare. In the fourth week of the experiment, a complete clinical picture of the development of chronic inflammatory generalized periodontitis was observed. Against the background of inflamed gums, the depth of periodontal pockets increased up to five-six millimeters. As a result, for the first time, radiological manifestations of the bone structure damage are revealed. Changes in the singular process were determined after the first two weeks of ligatures applying. One month later, the destruction reached 1/3 of the root length of the animal tooth.

Thus, the presented model of CGP has the following significant advantages necessary for carrying out: it provides the reproduction of inflammatory changes and the progression of structural and functional disorders in periodontal tissues, bone tissue lesions. Conformity of clinical and morphological features which demonstrate a pronounced clinical and pathological pattern inherent in chronic generalized periodontitis indicate that the model can be used for the study of modern means and technologies for the treatment of chronic generalized periodontitis, namely therapeutic, surgical and physiotherapeutic methods. The inflammation begins from the surface of the gums, gradually affecting the lower layers, where at different stages it is possible to study the signs of the lesion and the corresponding degree of development of chronic periodontitis.

Despite the above advantages, this model has some drawbacks. In some cases, the inflammation is of a local character, namely in places where metal ligatures are applied. Manifestations of pathology without generalization and development of pictures of pathological process were also observed.

In experimental dentistry results of **drug-induced models of reproduction of chronic periodontitis** in experimental animals are also given. For example, scientists of the Institute of Dentistry of NAMSU conducted an experiment aimed at studying the effect of a vitamin K antagonist (warfarin) on the structure of the gums and the reproduction of periodontitis in rats [6]. This is an example of drug-induced models of chronic periodontal reproduction, respectively, at the expense of the drug-induced variant of periodontal reproduction [2].

Mature rats, which were administered warfarin for 50 days, were selected for the experiment. Under the action of warfarin, glycosaminoglycan indices of the oral mucosa did not change significantly, but in the bone tissue of the alveolar process this index decreased by 15%. Compared to intact animals, collagen destruction was observed as a result of these changes. An increased concentration of sialic

acids was found in the serum of animals, which testified to the development of inflammatory processes in tissues (including periodontium). The introduction of warfarin increased the processes of bone resorption and activation of osteoclast functional activity. In the loose connective tissue of the mucous membrane of the cheek a mildly pronounced swelling processes were observed, collagen fibers thickened sharply, lymphocytes near the blood vessels were often found. The blood vessels are not structurally altered, but their walls are thickened due to the swelling present around cells and connective tissue fibers.

The following features obtained in experimental animals demonstrate the pathogenetic features of periodontal development in vitamin K avitaminosis. This is accompanied not only by biochemical abnormalities, but also by changes in physiological and histological nature in all tissues of the periodontium (including bone). Tested experimental model of periodontitis has significant drawbacks, which makes it impossible to use it in the modeling of chronic generalized periodontitis. The absence of serous purulent inflammation and its markers, the development of morphological manifestations of lesions observed over a long period of time, make this model necessary for the study of only certain links in the development of CP pathogenesis. The study of the drugs usage for its therapy in laboratory studies, without the use of other models of CGP is considered to be insufficient by most authors.

CONCLUSION

1. Clinical signs of local chronic periodontitis were observed in age-related, traumatic, and chronic stress-induced models. The results of the experiments were effective in describing the clinical features of the pathological process. This was evidenced by the appearance of periodontal pockets, the main feature of local periodontitis, which was observed in both cases experiments. With respect to morphological changes, it was visually manifested by hyperemia, edema of the gums and interdental papillae. In the course of chronization, these disorders were supplemented by pathology of the tooth-gingival attachment, retraction of the tooth, baring of its neck, separation of the interdental papillae. Long-term effects of pathological factor on tissues have been identified and described. The above changes tended to stabilization, spread and advancement of the process not only in periodontal tissues, but also in the area of the dental tissues proper and the transition of inflammatory disease into chronic lesions of the soft and bone structures. The lesion of the alveolar processes of the jaw gradually leads to a complete loss of teeth, just as in clinical setting.

2. It can be argued that progress in dentistry to some extent depends on experimental studies on descriptive models of pathology. The results of the descriptive models provide only fragmentary information on the study of the selected disease, restricting the ability to effectively correct the effects of individual pathogenetic factors. Choosing a particular model one should study the extent of the lesion, the periodization of the pathological process at different stages, substantiate treatment methods, and in the initial stages of periodontitis, this gives the opportunity to justify the development of regenerative therapies, the study of the impact of a single factor or the option of prophylactic prevention of chronic parodontitis.

Conflict of interests. The authors declare no conflict of interest.

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