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# MORPHOLOGICAL CHANGES IN PERIODONTAL TISSUES OF RATS IN THE EXPERIMENTAL MODEL OF TYPE 2 DIABETES MELLITUS

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Diabetes mellitus is one of the most common endocrine diseases, which prevalence is growing rapidly every year. The main pathogenetic factor of diabetes mellitus is persistent hyperglycemia and changes in the vascular walls of the microcirculatory bed. This leads to morphofunctional changes in the vascular wall, impaired permeability and trophism with progressive deterioration of hemodynamics and profound dystrophic changes, and, consequently, the inflammatory process's development. In the microcirculatory bed of the periodontium in patients with diabetes mellitus, there are pronounced changes in biochemical parameters of the blood and disturbed homeostasis, reduced resistance of periodontal tissues. This leads to increased exposure to periodontal pathogenic microflora, disrupts the integrity of the tooth-epithelial attachment, resorption of the cortical plate and the interdental septum, leading to tooth loss. The study of morphological changes in periodontal tissues of white Wistar rats in the conditions of experimental modelling of Type 2 diabetes mellitus is of great informational importance. This contributes to the development of measures aimed at preventing, early diagnosis, and effective treatment of periodontal diseases in patients with type 2 diabetes, especially in children and adolescents. Histological examination of morphological changes in periodontal tissues obtained with a microscope may be of practical use in future studies, serve to develop diagnostic, therapeutic and preventive measures for periodontal disease in children and adolescents with type 2 diabetes mellitus.

**Key words:** diabetes mellitus, streptozotocin, pathogenetic mechanisms, periodontium, periodontal changes.

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# МОРФОЛОГІЧНІ ЗМІНИ ТКАНИН ПАРАДОНТУ ЩУРІВ ПРИ ЕКСПЕРИМЕНТАЛЬНОМУ ЦУКРОВОМУ ДІАБЕТІ 2 ТИПУ

Цукровий діабет є одним із найбільш розповсюджених ендокринних захворювань, поширеність якого досить стрімко зростає з кожним роком. Основним патогенетичним фактором цукрового діабету є стійка гіперглікемія та зміни в стінках судин мікроциркуляторного русла, що призводить до морфофункціональних змін судинної стінки, порушення їх проникності та трофіки з прогресуючими погіршення гемодинаміки та поглибленими дистрофічними змінами, та, як наслідок, до розвитку запального процесу. У хворих на цукровий діабет, в мікроциркуляторному руслі пародонту відмічаються виражені зміни, оскільки змінюються біохімічні показники крові та порушується гомеостаз, знижується резистентність тканин пародонту, що призводить до посилення впливу пародонтопатогенної мікрофлори, порушується цілісність зубоепітеліального прикріплення, відбувається резорбція кортикальної пластинки та самої міжзубної перегородки, що може призвести до втрати зуба. Вивчення морфологічних змін тканин пародонту білих лабораторних щурів лінії Вістар, в умовах експериментального моделювання цукрового діабету 2 типу, має важливе інформаційне значення та сприяє розробці заходів, спрямованих на профілактику, ранню діагностику та ефективне лікування захворювань тканин пародонту у хворих людей на цукровий діабет 2 типу, що особливо актуально в дитячому та підлітковому віці. Гістологічне дослідження морфологічних змін тканин пародонту, що були отримані за допомогою мікроскопу, можуть мати практичне застосування у майбутніх дослідженнях, слугувати розробці діагностичних, лікувальних та профілактичних заходів щодо захворювань тканин пародонту у дітей та підлітків, хворих на цукровий діабет 2 типу.

**Ключові слова:** цукровий діабет, стрептозотоцин, патогенетичні механізми, пародонт, пародонтальні зміни.

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Diabetes mellitus (DM) is one of the most common endocrine diseases. According to the WHO, the number of people with DM in 2020 was 151 million, and by 2025 this figure is expected to increase to about 300 million people [10]. This problem is also relevant for Ukraine, where there is also an increase in this pathology. About 70 % of patients are in a state of chronic decompensation of DM, regardless of its type [3]. It should be noted that the prevalence of type 2 DM is growing rapidly. The β-cells of the pancreas produce enough insulin, but the body's tissues lose the ability to receive its specific signal.

The main pathogenetic factor of diabetes is persistent hyperglycemia, which often leads to the development of severe complications such as polyneuropathy, microangiopathy, nephropathy, retinopathy, encephalopathy. Special attention to the genesis of diabetes complications is paid to morphofunctional changes in the vascular wall. Pathological changes in blood vessels in diabetes mellitus are a universal morphogenetic sign of diabetes complications, creating conditions for the development and progression of periodontal disease [10, 16]. The results of epidemiological studies have shown a high prevalence of periodontitis among patients with diabetes mellitus [2]. The risk of developing diabetes in children and

young adults is by 2.5–3.5 times higher than in people with a light medical history. At the same time, periodontal tissue lesions were recorded in approximately 51.2 % of children with diabetes [7].

During this disease, pronounced changes are noted in the microcirculatory bed of periodontal disease, since the biochemical parameters of blood change and homeostasis is disrupted, which leads to the appearance of various forms of periodontitis, from its initial stage of gingivitis to periodontitis [9]. The resistance of periodontal tissues decreases, which leads to increased exposure to periodontal pathogenic microflora. In patients with diabetes, there is a decrease in periodontal endurance with the development of diabetic periodontitis; osteoporosis progresses, and the ability to regenerate bone tissue decreases, inflammatory changes in the mucous membrane are formed [1]. The integrity of the tooth-epithelial attachment is violated, there is resorption of the cortical plate and the interdental septum, leading to tooth loss [6, 10]. The gum mucosa undergoes degenerative-dystrophic changes, characterised by impaired capillary permeability, deterioration of trophic in the microcirculatory bed of the periodontium, the progression of dystrophic and inflammatory processes. Their main reason is a violation of hemodynamics, reduced oxygen supply to periodontal tissues and deterioration of metabolic processes in these tissues. The obtained data on morphological changes of periodontal tissues studied in the experimental model of type 2 diabetes can be used in future studies to develop diagnostic, therapeutic, and preventive measures for periodontal disease in children and adolescents with type 2 DM.

**The purpose** of the work was to study and describe the morphological changes in the soft tissues of the periodontium of laboratory rats on the background of experimental type 2 diabetes mellitus to create, in the future, preventive measures to prevent complications of periodontal disease.

**Materials and methods.** The experimental study was performed on 26 white laboratory rats of the Wistar line weighing 180–230 g, which were kept in the vivarium of the Bogomolets National Medical University (Kyiv). The study was performed on the basis of the Institute of Pathology of the Bogomolets National Medical University. The experimental animals were divided into 2 groups. The control group (6 animals) was kept on a standard vivarium diet, which included dry mixed plant feed in briquettes, corn (100–200 g) and water (400 ml).

The main group included 20 experimental animals in which type 2 diabetes was modelled by keeping on a High Fat Diet (HFD) [8]. Animal fat (10 % of the feed weight) was added to the standard vivarium diet, and a single intraperitoneal administration of streptozotocin (STZ, "Serva", Germany, IP, at a dose of 40 mg/kg) [8]. STZ was dissolved in citrate buffer solution (pH 4.6) [5].

Prior to the study, each animal was weighed, labelled, and measured using anthropometric data. Repeated weighing and measurement of anthropometric data of experimental animals of both groups were performed on the 11th and 28th days of the experiment.

All manipulations with animals were carried out in accordance with the Law of Ukraine No. 3447-IU "On Protection of Animals from Cruel Treatment" and the European Convention for the Protection of Vertebrate Animals used in Experimental Research and Other Scientific Purposes.

Gum tissue of experimental animals was used as material for histological examination. On the 28th day of the experiment, it was taken using a sharp scalpel and immediately fixed in 10 % formalin solution. After dehydrating in alcohols of increasing concentration and pouring into paraffin, serial sections with a thickness of 5 microns were made from each block, stained with hematoxylin and eosin according to conventional methods. Further research was conducted on the basis of the National Scientific Center "M.D. Strazhesko Institute of Cardiology". The preparations were studied and photographed under a microscope MICROS Austria MCX 100 ED, magnification: eyepiece 10, lens 4 with a numerical aperture of 0.10; eyepiece 10, lens 10 with a numerical aperture of 0.25; eyepiece 10, lens 20 with a numerical aperture of 0.4; eyepiece 10, lens 40 with a numerical aperture of 0.65. Rats with the highest blood glucose levels were selected from the main group of experimental animals. They were administered a single STZ dose of 40 mg/kg and then kept on a high-calorie diet (HFD+STZ group). The onset of type 2 DM occurred on day 11 of the experiment after STZ administration. Severe diabetes mellitus was performed only on the 28th day of the experiment.

On day 1 of the experiment, a 5 % glucose solution was administered to experimental animals of both groups to determine plasma glucose concentration and test for glucose tolerance. Blood glucose concentration was determined using a glucose meter with test strips ("One Touch Ultra Plus Flex", Switzerland). On day 11 of the experiment, rats were re-measured blood glucose. On the 28th day, the final measurement of glucose concentration and test for insulin resistance to glucose were performed.

Rats in the main group, which had the highest blood glucose levels (12 animals), were tested for glucose tolerance to diagnose impaired glucose tolerance (prediabetes) and diabetes. After six hours of fasting, selected rats of the main group were injected intraperitoneally with insulin at a dosage of 0.175

IU/kg (at a dosage of 1 g per 1 kg of body weight). Blood was taken from the tail vein after 15, 30, 45, 60, 120 min [11].

After determining glucose tolerance, experimental animals of the main group were divided into two subgroups, which included animals with a blood glucose concentration higher than 15 mmol/L (HFD+STZ>15) and animals with a glucose concentration of less than 15 mmol/L (HFD+STZ<15). A sampling of material for histological examination was performed in an experimental group of animals whose blood glucose levels were higher than 15 mmol/L (HFD+STZ>15).

**Results of the study and their discussion.** On the 11th day of the experiment, rats showed a significant increase in blood glucose concentration, from 5.6±0.2 to 9.8±0.3 mmol/L ($p \leq 0.01$), in contrast to the values at the beginning of the experiment, which confirms the presence of long-term hyperglycemia and the onset of Type 2 diabetes mellitus (table 1).

Table 1

**Changes in blood glucose concentration of experimental rats in the dynamics of the experiment**

| Terms of the study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| At the beginning of the experiment | | | 11th day | | | 28th day | | |
| Cage | Rat | Glucose level in mmol/L | Cage | Rat | Glucose level in mmol/L | Cage | Rat | Glucose level in mmol/L |
| 1 | 1 | 5.2 | 1 | 1 | 7 | 1 | 1 | 5.9 |
| | 2 | 4.8 | | 2 | 5.1 | | 2 | 4.5 |
| | 3 | 3.9 | 2 | 2 | 5.9 | | 3 | 6.2 |
| | 4 | 3.9 | | 5 | 5.6 | | 4 | 7.2 |
| 2 | 1 | 6.5 | 3 | 3 | 9.8 | 2 | 1 | 6.2 |
| | 2 | 22.4 | | 4 | 6.4 | | 2 | 31.7 |
| | 3 | 5 | 4 | 1 | 6.3 | | 3 | 5.4 |
| | 4 | 8.9 | | 2 | 6.2 | | 4 | 5.5 |
| | 5 | 28.7 | 5 | 1 | 4.7 | 3 | 1 | 29 |
| 3 | 1 | 4 | | 2 | 5.7 | | 2 | 8.4 |
| | 2 | 4.4 | 6 | 2 | 5.5 | | 3 | 15.2 |
| | 3 | 7 | | 3 | 5.7 | 4 | 1 | 5.8 |
| | 4 | 4.9 | 7 | 4 | 4.8 | | 2 | 6.2 |
| 4 | 1 | 19.8 | | 5 | 3.7 | | 3 | 7.2 |
| | 2 | 5.8 | 8 | 2 | 4.7 | | 4 | 7.3 |
| | 3 | 4.2 | | 5 | 4.9 | 5 | 1 | 5.6 |
| | 4 | 3.6 | 9 | 2 | 5.4 | | 2 | 6.9 |
| | 5 | 4.3 | | 4 | 5.2 | | 3 | 6.5 |
| 5 | 1 | 4.8 | 10 | 1 | 9.3 | | 4 | 9.8 |
| | 2 | 5.5 | | 3 | 5.8 | | | |
| | 3 | 3.3 | | | | | | |
| | 4 | 4.3 | | | | | | |
| | 5 | 3.8 | | | | | | |
| 6 | 1 | 3.6 | | | | | | |
| | 2 | 4.3 | | | | | | |
| | 3 | 4 | | | | | | |
| | 4 | 3.8 | | | | | | |
| | 5 | 3.6 | | | | | | |
| 7 | 1 | 4.4 | | | | | | |
| | 2 | 3.9 | | | | | | |

A significant increase (more than 5 times) in the blood glucose concentration of experimental animals from 5.6±0.2 to 31.7±0.6 mmol/l ($p \leq 0.01$) on the 28th day of the experiment compared to previous values indicates the rapid development of type 2 diabetes.

Apparent changes can be seen in the study of glucose levels in the blood of experimental animals during a test for glucose tolerance. The glucose level in venous blood for more than 10.1 mmol/L indicated the development of a stable form of type 2 diabetes. Glucose concentration from 6.8 to 10.0 mmol/L showed impaired glucose tolerance and the possibility of diabetes mellitus occurrence in experimental rats shortly (table 2).

Table 2

**Results of the glucose tolerance test in selected rats of the main group depending on the time**

| Rat | 0 min. | 15 min. | 30 min. | 45 min. | 60 min. | 120 min. |
|---|---|---|---|---|---|---|
| | in mmol/L | | | | | |
| 1 | 7.1 | 5.7 | 5.4 | 4.5 | 5.4 | 3.3 |
| 2 | 6 | 6.8 | 4.8 | 2.6 | 4.3 | 3.7 |
| 3 | 6.7 | 7.8 | 10.5 | 6.3 | 5.4 | 5 |
| 4 | 6.6 | 10.2 | 13.7 | 8.4 | 6.6 | 6.9 |
| 5 | 7.1 | 13.8 | 7.3 | 10.7 | 8.2 | 7.2 |
| 6 | 7.2 | 4.6 | 3.5 | 7.8 | 6 | 4.7 |
| 7 | 6.2 | 8.9 | 8.4 | 6.3 | 5 | 4.1 |
| 8 | 15.3 | 14 | 14.8 | 12.4 | 9.3 | 7.3 |
| 9 | 31.7 | 24.8 | 27.3 | 26.4 | 21.4 | 16.5 |
| 10 | 29 | 22.3 | 20.1 | 30.9 | 12.1 | 16.8 |
| 11 | 8.4 | 12.3 | 10 | 7 | 6.7 | 9.9 |
| 12 | 7.2 | 4.6 | 5.7 | 4.9 | 4.8 | 4.3 |

It should be noted that the body weight and anthropometric parameters of experimental animals at the beginning and during the experiment did not differ much, which may indicate that type 2 diabetes is not always accompanied by weight gain and obesity. The results of histological examination revealed several disorders and vascular changes in periodontal tissues of rats in which type 2 diabetes mellitus was experimentally simulated.

Microscopic examination of the gingival margin's mucous membrane and the gums' free part revealed pronounced acanthosis and uneven hyperkeratosis with focal desquamation of the stratum corneum (fig. 1).

Vacuolization of the cytoplasm of epithelial cells and endothelial cells of arterioles is pronounced in the area of the external epithelium of the gingival mucosa (fig. 2).

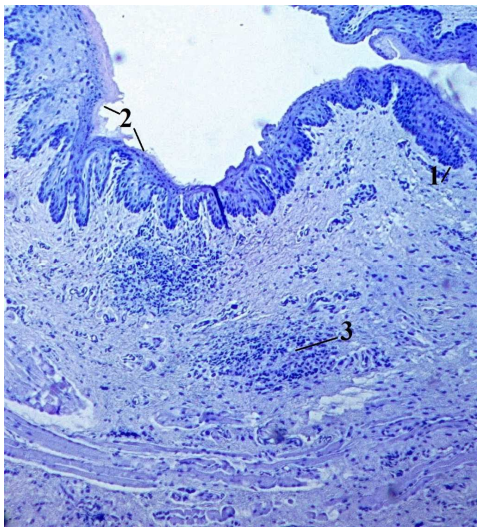


Fig. 1. The free part of gums and gingival margin of rats with type 2 diabetes mellitus: 1– acanthosis 2– uneven hyperkeratosis with focal desquamation of the stratum corneum; 3 – focal mixed cell infiltration. Hematoxylin and eosin staining. Magn. x 40.

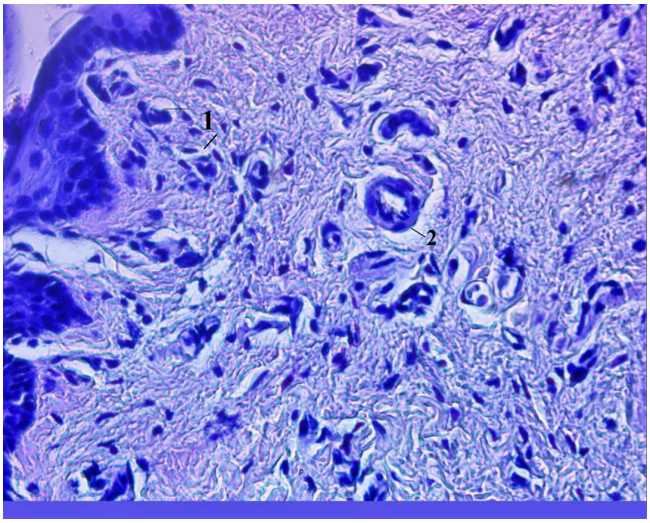


Fig. 2. The mucous membrane of the gums of rats with experimental type 2 diabetes mellitus: 1– angiomatosis; 2 – perivascular oedema of the arteriole wall. Hematoxylin and eosin staining. Magn. x 400.

Parakeratosis and focal desquamation were observed in some areas of the gum epithelium. The epithelium of the zone of gingival attachment is generally regular in structure, but there were areas of uneven thinning. In the thickness of the own plate of the gum mucosa, there are areas of diffuse oedema with focal angiomatosis (fig. 2, fig. 3). There is also a thickening of the arteriole walls due to plasma permeation with uneven hyperemia, focal mixed cell infiltration.

Such signs indicate the presence of chronic inflammation in the periodontal tissues. The focal opening of reserve capillaries is a sign of increasing the amount of circulating blood, enriching them with oxygen to the compensatory improvement of metabolism. Activation of reserve capillaries is also observed in the own plate of the gingival mucosa and areas adjacent to thickened arterioles.

An attached part of the gums, represented by multi-layered squamous epithelium, in which stratum corneum is thinner, with the focal proliferation of the basal layer. Areas of diffuse oedema with pronounced focal angiomatosis in the form of capillaries placed in groups were observed in the thickness of the gingival mucosal plate. The periodontium is swollen, there is uneven hyperemia of blood vessels, focal dilatation with focal perivascular lymphohistiocytic infiltration. There is an uneven thickening of the capillary walls due to their plasma permeation, as well as areas of perivascular haemorrhage. The bottom of the gingival sulcus has signs of lymphohistiocytic infiltration and sclerosis, which indicates the formation of gingival pockets and the formation of keratin cysts (fig. 4).

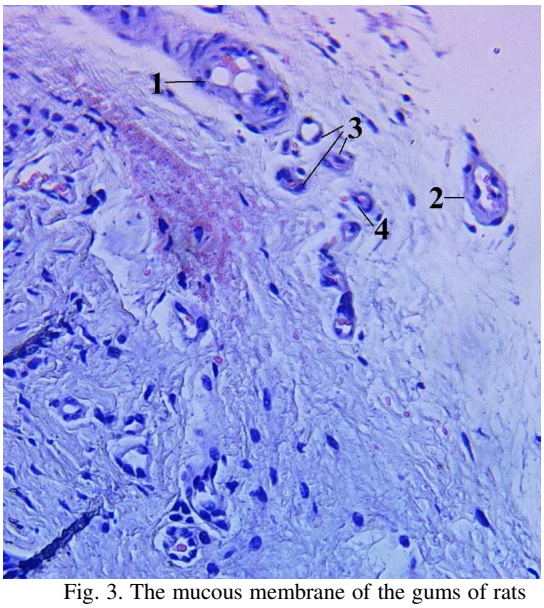


Fig. 3. The mucous membrane of the gums of rats with experimental type 2 diabetes mellitus: 1 – pronounced vacuolation of arterial endothelial cells; 2 – plasma permeation of the arteriole wall; 3 – angiomatosis; 4 – increased permeability of vascular walls. Hematoxylin and eosin staining. Magn. x 400.

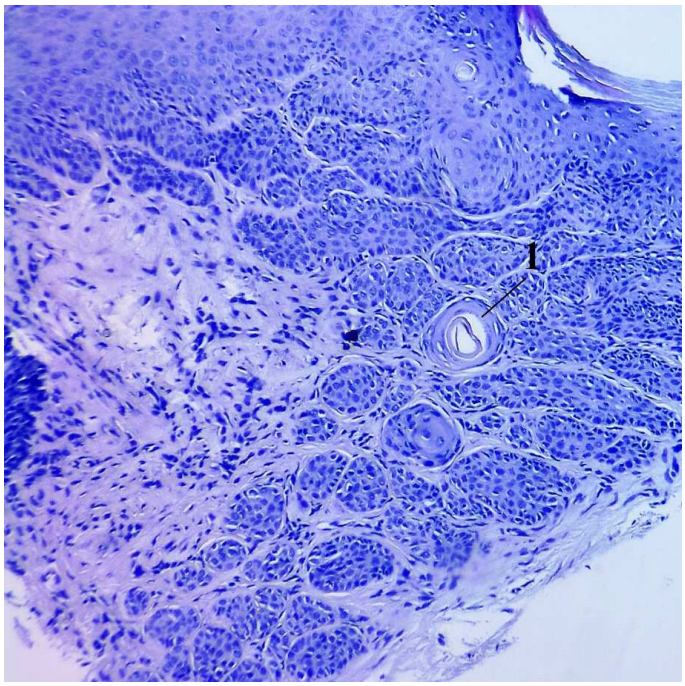


Fig. 4. Formation of keratin cysts. 1– keratin cyst. Hematoxylin and eosin staining. Magn. x 200.

Thus, the work carried out allowed us to obtain several results that coincide with the results of other studies. An important place among endocrine diseases is occupied by type 2 diabetes because it is one of the most common endocrine pathologies today [10]. According to the study results, children and adolescents with type 2 diabetes mellitus have pronounced inflammatory-dystrophic processes in periodontal tissues, atherogenic disorders of plasma lipids, which were considered risk factors for microcirculatory diseases of periodontal tissue [7]. A solution to this problem is to simulate diabetes mellitus in experimental animals and its further study. This can help obtain data on morphological changes in periodontal tissues in type 2 diabetes mellitus and has practical application in research. One of the most popular methods of modelling diabetes in experimental animals is the administration of chemicals. Streptozotocin is among the most commonly used compounds, which in the appropriate dose can cause diabetes of both the first and second type [16]. Keeping animals on a high-calorie diet for three weeks and STZ administration leads to the formation of an adequate model of type 2 diabetes. This is confirmed by increased blood glucose concentration and characteristic changes in glucose tolerance and immunoresistance tests [5]. Histological examination of rats' periodontium allowed us to investigate the morphological changes occurring in the periodontal tissues in type 2 diabetes. Impaired microcirculation in periodontal tissues is accompanied by abnormalities in the growth and regeneration of blood vessels. Deterioration of hemodynamics and trophic disorders leads to a number of inflammatory and dystrophic processes and changes in periodontal tissues. Morphological changes in trophic disorders in diabetes mellitus can be the basis for finding ways to correct structural changes in the dental and maxillofacial apparatus in experimental dentistry [6]. Patients with diabetes mellitus require careful oral care and adequate comprehensive prevention and simultaneous treatment of the underlying disease and dental complications, including periodontal diseases [10]. The study of such changes and their features will contribute to the development of the most appropriate diagnostic, therapeutic and preventive measures for periodontal tissue diseases in children, adolescents and young people with type 2 diabetes.

## Conclusion

Thus, the development of type 2 diabetes mellitus in laboratory rats is confirmed by several morphological changes in the soft periodontal tissues of experimental animals. First of all, these are changes in the walls of the vessels of the microcirculatory bed with the subsequent violation of their permeability and, consequently, the deterioration of periodontal trophism in general. Progressive deterioration of hemodynamics also leads to the deepening of dystrophic changes and the development of inflammatory processes that gradually disrupt the cytoarchitectonics of the periodontium. A detailed study of such disorders by modelling experimental diabetes can help solve the problems of diagnosis, prevention and treatment of periodontal disease in patients with type 2 diabetes.

*Prospects for further research. The obtained data on morphological changes of periodontal tissues studied in the experimental model of type 2 diabetes can be used in future studies to develop diagnostic, therapeutic, and preventive measures for periodontal disease in children and adolescents with type 2 diabetes.*

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