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THE HISTOCHEMICAL FEATURES OF THE ENDOTHELIUM OF THE TOOTH-ALVEOLAR COMPLEX IN INFLAMMATION AND OSTEOPOROSIS

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ГИСТОХИМИЧЕСКИЕ ОСОБЕННОСТИ ЭНДОТЕЛИЯ СОСУДОВ ЗУБОАЛЬВЕОЛЯРНОГО КОМПЛЕКСА ПРИ ВОСПАЛЕНИИ И ОСТЕОПОРОЗЕ

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The results of immunohistochemical studies of the pulpal state and vascular endothelium of the dental alveolar complex are presented in the experimental modeling of periodontitis and osteoporosis in sheep. The endothelial structural parameters of PD in animals in the gums of the upper and lower jaws differ and affect the length, thickness of cells, number of mitochondria, Golgi complex, reticulum of the endothelium, relationship between the nucleus and cytoplasm, and amount of heterochromatin in the nucleus. In periodontitis, pathological changes are noted in the endothelial circle, as well as in pericytes; this is manifested by a complex vascular-tissue reaction of the microcirculatory bed of periodontal tissues with a violation of the rheological properties of the blood, combined with the formation of exudate and an inflammatory cell infiltrate. In the early period after the formation of the model of experimental osteoporosis, slight thickening and straightening were observed in the Korff fibers; at 180 days, the APHF exhibited a more linear structure, occasionally forming a finely mottled network that resembled a mosquito net. At 1 year of observation, there was a lack of Korff fibers in the primary substance of the pulp, and significant thickening of the argyrophilic membranes in the vascular endothelium; these are signs of impairment in the metabolism of the tooth pulp.

Keywords: osteoporosis, periodontitis, experiment, endothelium

Представлены результаты иммуногистохимического исследования пульпы и эндотелия сосудов зубоальвеолярного комплекса при экспериментальном моделировании пародонтита (ПД) и остеопороза (ОП) у овец. Эндотелиальные структурные показатели при ПД у животных в сосудах десен верхней и нижней челюсти различаются и затрагивают длину, толщину клеток, количество митохондрий, комплекс Гольджи, ретикулум эндотелия, взаимосвязь ядра и цитоплазмы и количество гетерохроматина в ядре. При ПД патологические изменения отмечены не только в эндотелиальном круге, но и в перицитах, что проявляется комплексной сосудисто-тканевой реакцией микроциркуляторного русла тканей пародонта с нарушением реологических свойств крови, образованием экссудата и воспалительного клеточно-го инфильтрата. В ранние сроки после формирования модели экспериментального ОП наблюдались незначительное утолщение и выпрямление волокон Корфа, а к 180 суткам эксперимента аргирофильные волокна становились более выпрямленными, иногда образовывая мелкопетлистую сеть, похожую на москитную сетку. В срок наблюдения 1 год в части препаратов наблюдалось отсутствие волокон Корфа в основном веществе пульпы, значительное утолщение аргирофильных мембран в эндотелии сосудов как признак ухудшения обмена веществ в пульпе зуба.

Ключевые слова: остеопороз, пародонтит, эксперимент, эндотелий

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APhF – Argyrophilic Fibers
BM – Basal Membrane
DAC – Dental Alveolar Complex
DAS – Dental Alveolar Segment

IHCS – Immunohistochemical Study
OP – Osteoporosis
PD – Periodontitis

Inflammatory periodontal disease (PD) is an urgent problem in dentistry. Due to its social importance, PD occupies a special role in medicine; according to recent data, up to 90 % of the population exhibit PD of mild, moderate, and severe degrees [1, 2]. The age spectrum of PD disease primarily covers a period of 25–35 years; with increased age, severe forms of PD are increasingly observed. Although the nosology of PD has been involved a large number of studies, there is no consensus regarding its etiology and pathogenesis. In recent years, scientists have speculated that a cause of PD involves circulatory disorders; in particular, dystrophic processes develop as a result of atherosclerotic changes in blood vessels [3, 4]. Notably, pathomorphological studies revealed significant changes in the walls of the periodontal arteries (perivascular sclerosis, thickening of the walls of blood vessels, narrowing of the lumen, and/or hyalinosis).

In the scientific literature, a pathological role of hypoxia in PD has been highlighted. Multiple studies have revealed a reduction in oxidation-reduction potential in periodontal pathology, as evidenced by the accumulation of weakly oxidized products in tissues; as a result of this change, the barrier function of periodontal tissues decreases and pathological phenomena characteristic of PD (e.g., gingivitis, bone resorption, and pathological periodontal pocket formation) occur [5]. Of particular interest is the study of the histochemical features of periodontal tissues in a chronically progressing systemic metabolic disease of the skeleton: osteoporosis (OP), which is characterized by a reduction in bone density, a violation of microarchitectonics, and an increase in fragility.

The aim of this study was to perform a histochemical evaluation of the structure of the vascular endothelium in periodontal tissues in inflammation and OP.

Material and Methods. Experimental research was performed in two stages; experimental animals were mature sheep of the North Caucasian breed (18 animals, including 10 females and 8 males). During the study, two experimental models were created in animals: PD and OP.

During the first stage of the experiment, four animals with unchanged periodontium (control group) and four with obvious signs of disease (the main group) were selected for the study. To form the experimental PD model in the main group, intramuscular methyluracil was administered to the animals at a dose of 60 mg/kg, two times per day for 4 weeks. Local lesioning of the gingiva and tissues of the vestibule of the mouth was performed by using appliques of a suspension of bee venom at a dose of 2 mg/kg of animal weight. Each animal received five applications with a 5-day interval between each application. Dental alveolar segment (DAS) (blocks) were removed under general anesthesia (Zoletil 50) at 2, 14, and 60 days after the start of the study. The isolated blocks were fixed for 7 days in 10 % neutral buffered formalin, a Bowen fixer for trichrome staining, and an Immunophix fixer for immunohistochemistry (IHC; Biovitrum, Russia). After fixation, the blocks were decalcified in a 5 % solution of trichloroacetic acid with daily changes of the solution for 5 days. After decalcification, the blocks were subjected to dehydration through serial exposure to increasing concentrations

of alcohol and xylene, after which they were immersed in Histomix histological medium (BioVitrum, Russia), using a closed-type histological processor Tissue-Tek VIP™ 5 Jr and the paraffin filling station Tissue-Tek® TEC™ 5 (Sakura, Japan). Histological sections of 3–5-μm thick were made from the resulting blocks by using a microtome and a table for the preparation of histological sections (Bio-Optica, Italy); the sections were stained with dyes (Bio-Optica and BioVitrum) on an automatic Prisma™ multi-stainer (Sakura, Japan). The painted sections were enclosed in the mounting environment of Biomount (BioVitrum). Staining of sections for review purposes was performed with hematoxylin and eosin; collagen fibers were stained by the Akimchenko and Masson methods. To identify antigens in tissue cells, IHC was performed with antibodies: monoclonal mouse antibodies to vimentin (V9), α-smooth muscle actin-α-SMA (1A4), CD34 (QEnd/10), epithelial membrane antigen (Anti-EMA, E29) (Spring Bio Science, USA). IHC reactions were performed with paraffin sections by using the highly sensitive Reveal biotin-free polyvalent DAB imaging system (Spring Bio Science). The intensity of IHC in each sample was monitored under a microscope.

For the second stage of the study, 10 sheep were divided into two groups: basic (six animals) and control (four animals). In the main group, an experimental model of OP was induced under general anesthesia (Zoletil 50); ovariectomy was performed, followed by intramuscular injection of dexamethasone for 3 months [9]. Tissue collection was performed under general anesthesia in the area of the lower incisors (hooks), by isolating DAS under general anesthesia after 90 days, 180 days, and 1 year after the start of the experiment. In the control group, the corresponding dental alveolar complex (DAC) in the intact animals was examined. The isolated blocks were fixed for 8–10 days in a 12 % solution of neutral formalin, decalcified in a mixture of equal volumes of 10 % formic and 8 % hydrochloric acid, washed under running water, immersed in alcohol solutions of increasing concentration, and poured into celloidin. Sections 3–5-μm-thick were stained with hematoxylin and eosin, then impregnated with silver by the Fout method. When APhF was detected in the decalcified blocks, slices were prepared to assess the state of the cellular elements of the tooth pulp by impregnating with silver nitrate by the Bilshovsky-Gross and Masson methods, which enabled detection of both collagen and APhF.

Data processing: All results were statistically evaluated by using one-way analysis of variance and Newman-Keuls multiple comparisons in Primer of Biostatistics 4.03 for MS Windows (USA). Differences were considered valid for $p < 0.05$. The definitions of histological structural parts and formations of the DAC were as given by the international nomenclature Terminologia Histologica (2009).

Experimental studies were performed in compliance with the International Principles of the European Convention on the Protection of Vertebrates used for Experiments and Other Scientific Purposes (Strasbourg, 1986), in accordance with the principles of good laboratory practice (National Standard, Good Laboratory Practices, GOST R 53434-2009), International Recommendations on Biomedical Research Using Animals (1985), the Rules of Laboratory Practice in the Russian Federation (Order of the Ministry of Health of the Russian Federation № 267 on 19.06.2003), General Ethical Principles of Animal

Experiments (Russia, 2011), and the approval of the ethics committee regarding vivarium conditions in a federal state budgetary educational institution of higher education (Stavropol State Agrarian University). Research work was performed within the framework of the State task of the Ministry of Health of the Russian Federation.

Results and Discussion. Structural and ultrastructural studies of the endothelium in the first series of experiments in the control group (normal) revealed cells with a polygonal shape, closely adjoined with each other; cytochemical reactions revealed the presence of glycogen in these cells in large quantities. The cell nuclei had an elongated shape; in the nuclei, heterochromatin was predominate. On the surface of the walls of the vessels were microvilli, variable in number; most were long and broad. The numbers of organelles and pinocytosis vesicles in the cytoplasm were minimal. The microstructure of the endothelium was non-uniform, as there were both long and short endothelial cells. Long cells were primarily found in the gingiva of the upper jaw, with lengths of $18.4 \pm 3.15 \mu\text{m}$ to $130.7 \pm 9.45 \mu\text{m}$; the lengths of endothelial cells in the gingiva of the lower jaw were $70.2 \pm 2.15 \mu\text{m}$ to $100.9 \pm 6.75 \mu\text{m}$. The thickness of endothelial cells in the gingiva of the upper jaw was $66.0 \pm 4.65 \mu\text{m}$ to $105.5 \pm 10.8 \mu\text{m}$; in the gingiva of the lower jaw, it was $34.6 \pm 1.25 \mu\text{m}$ to $54.0 \pm 5.35 \mu\text{m}$. The area of endothelial blood vessels also exhibited significant differences (Table). The surfaces of endothelial cells were covered with paraplasm (glycoproteins). Pinocytosis

network was relatively well-represented. In the gingiva of the lower jaw, these structural formations were relatively minimal. Notably, collagen fibers were located between the capillaries, where single lymphocytes were detected. The layer of endothelial cells typically allows passage of a small number of shaped elements; on this basis, the endothelium of the vessels of the tissues of the patient at the thirtieth day of the experiment only partially regulated transendothelial migration. Concomitantly, the endothelium of the vessels during chronic inflammation in the periodontium continues to regulate local processes of proliferation, migration into the wall of blood vessels, and the tone of blood vessels; thus, it plays an active role in local blood circulation, homeostasis, coagulation, and platelet activation.

Table

**Area of endothelial blood vessels
in control and PD animals, μm^2**

Days	Arterioles, $\text{M} \pm \text{m}$		Venules, $\text{M} \pm \text{m}$	
	Upper jaw	Lower jaw	Upper jaw	Lower jaw
Control	45.90 ± 3.15	45.90 ± 3.15	51.63 ± 5.55	51.63 ± 5.55
2 nd day	$29.10 \pm 2.80^*$	$25.44 \pm 1.71^*$	$41.93 \pm 4.70^{* \&}$	$30.13 \pm 2.59^*$
14 th day	$33.13 \pm 3.17^*$	$30.46 \pm 2.75^*$	$31.50 \pm 2.05^*$	$33.17 \pm 1.79^*$
60 th day	$35.49 \pm 1.45^*$	$33.16 \pm 1.27^*$	$34.25 \pm 2.44^*$	$32.25 \pm 2.35^*$

Note: the statistical significance of the differences with the control: * – $p < 0.05$; between the upper and lower jaws: & – $p < 0.05$.

vesicles were primarily located on the surface of the endothelium, and were predominant in the gingiva of the upper jaw, rather than in the gingiva of the lower jaw. In the main group (experimental PD) on the second day of observation, the capillaries were fenestrated, and the basal membrane (BM) of the endotheliocytes had a finely fibrillar structure. The thickness of the membrane in the gingiva of the lower jaw averaged $28.2 \pm 4.45 \mu\text{m}$ to $30.9 \pm 3.85 \mu\text{m}$; it was 32.9 ± 6.15 to $35.6 \pm 7.25 \mu\text{m}$ in the gingiva of the upper jaw. The outer side of the BM was covered with pericytes that were unevenly distributed, and were primarily found in the gingiva of the upper jaw; nerve endings were noted on the pericytes. The outer side of the capillaries was covered with relatively well-differentiated adventitial cells. By the fourteenth day of the experiment, cells of mesenchymal origin were found throughout the endothelium, most frequently including small, specialized and differentiated fibroblasts, fibroblasts, and myofibroblasts. Expression of the myofibroblast marker (α -SMA + cells) exhibited a fine and large-granular cytoplasmic pattern (Fig. 1). The immunoreactive material was localized in the form of granules, scattered throughout the cytoplasm of cells. The intensity of antigen expression in cells was intense; α -SMA + cells were spindle-shaped, with a centrally located nucleus. Smooth muscle cells expressed the antigen, and formed the middle portion of the blood vessels. By the thirtieth day of the experiment, the BM affected the entire capillary network, and the uneven structural BM characteristics negatively affected diffusion efficiency. At this time point, diffusion in the BM was more intense in the gingiva of the lower jaw, because it exhibited thinner BM than in the gingiva of the upper jaw. The number of mitochondria was elevated in the gingiva of the upper jaw and the endoplasmic (agranular)

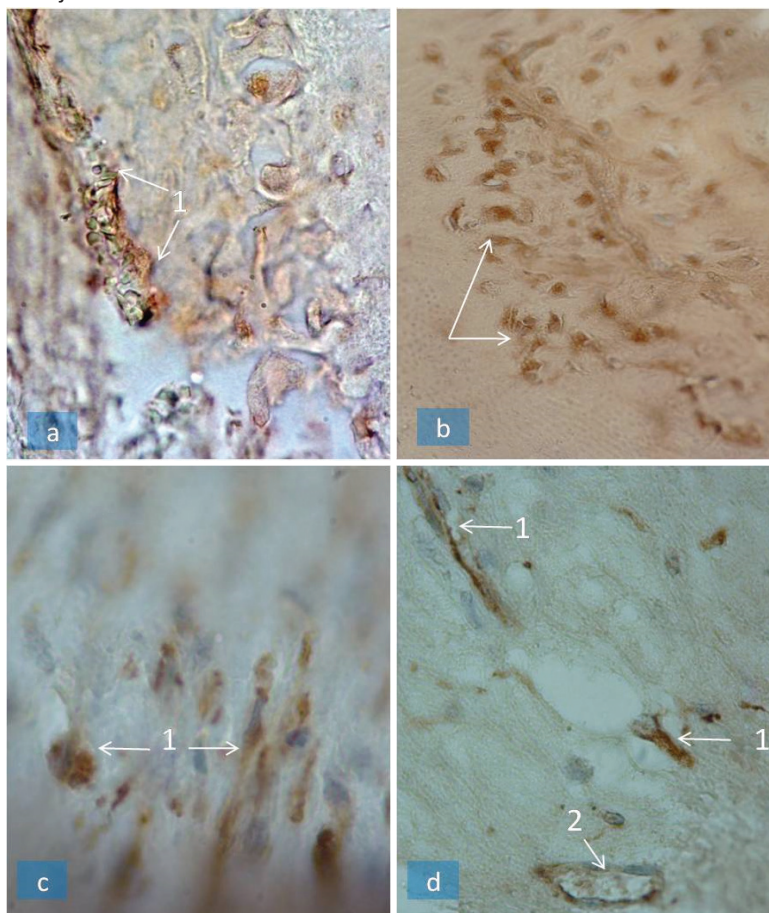


Fig. 1. Micro-preparations of the lower extremity (a, b) and upper jaw (c, d) in normal (b) and PD (a, c, d): a – expression of α -SMA + in medial arterioles (1). IHC reaction to α -smooth muscle actin. The reaction product is brown; b – expression of vimentin. IHC reaction to vimentin. The reaction product is brown (marked by arrows); c – expression of epithelial membrane antigen (1). IHC reaction to EMA. The reaction product is brown. OK. 10, v/v. 100; d – expression of synaptophysin (1) in neural neurons in neurosecretory vesicles (2). IHC reaction to synaptophysin. The reaction product is brown. Ok. 10, Obj. 100

In the second series of experiments (osteoporosis) in the control group, the fibrous component of the pulp was represented primarily by collagen fibers, with the greatest proportion of fibrous components in the crown and root of the tooth; the central portion exhibited a less fibrous structure and more abundant blood supply. On the periphery of the crown, thin spiraling tooth pulp passed through the odontoblast, Weyl, and subodontoblast layers, radially located and well-impregnated with argyrophilic fibers (APhF, radial Korff fibers). Entering the dentin, they were located mainly in the substance of dentin, close to dentinal tubules. In the central layers of the pulp, the APhF formed a fairly coarse-grained network (Fig. 2); closer to the periphery of the pulp, this network became finer. In addition to a delicate network of APhF, a network of collagen fibers was also observed in the pulp of the tooth. A thin membrane, consisting of APhF, was

located around the vessels in the pulp of the tooth. In addition, the vessels were surrounded by collagen fibers. In small vessels, both APhF and collagen fibers were located along the endothelium of the vessels; in larger vessels, these fibers traveled both along the vessels and circularly.

In the main group, by 90 days, as in the control group, all layers of pulp were expressed, the layer of Korff fibers was well-developed, and a thin network of APhF was revealed in the central sections of pulp. In isolated cases, we observed separate thickened and straightened Korff fibers and a slight vacuolization of the odontoblast layer. In areas where vacuoles were located, the Korff fibers traveled around them. Argyrophilic membranes around vessels, as a rule, were not thickened. On the boundary between the predentin and the pulp of the tooth, the Fleischmann film was observed; when treated with silver by Bilshov-Gross, this film was impregnated black. It appeared to arise from the fusion of APhF that entered the dentin. In one tooth of this group, single thickened and straightened Korff fibers and small denticles, surrounded by thin APhF, were simultaneously found in the pulp. Membranes around the vessels, as a rule, were not thickened.

When modeling OP at 180 days, teeth were encountered, in the pulp of which the layer of Korff fibers was weakly expressed; single thickened and straightened fibers were encountered. In the central sections of the pulp, a dense shallow-loop network of APhF was observed, similar to the appearance of a mosquito net (Fig. 3). Vessels were dilated and membranes around some were thickened. On some preparations, a layering of cloak dentin was observed in the form of dark lines passing over its entire surface (tangential fibers of Ebner), which was associated with enhanced calcification of primary dentin from the pulp side. The uneven deposition of secondary dentin clearly manifested in the lateral walls of the tooth root. In the pulp, vacuolization of the odontoblast layer was noted. Abnormal dentin formation was observed throughout, forming false wall-side denticles; these originated from the predentin, in the form of poorly organized irregular forms of structures in which there were no tubules (uncanalized denticles). In the resulting structures, the bodies of odontoblasts were visible, which comprised the source of denticle formation.

After 1 year, experimental changes were observed in the structure of APhF of the pulp of the teeth. In the tissue preparations, the quantity of Korff fibers was reduced and they were poorly impregnated. In the central sections of the pulp, changes in the APhF were manifested as a dense, finely meshed network, with fibers that were straightened and poorly impregnated. The vessels were dilated, and some surrounding membranes were thickened; occasionally, thick collagen fibers were observed entering the dentin. Collagen fibers of the tooth pulp, as well as APhF, both entering the dentin, participated in its basic formation. A slight ectasia of tubules was noted in the predentin and parapulp's dentin. Against the background of a complete absence of APhF, there were

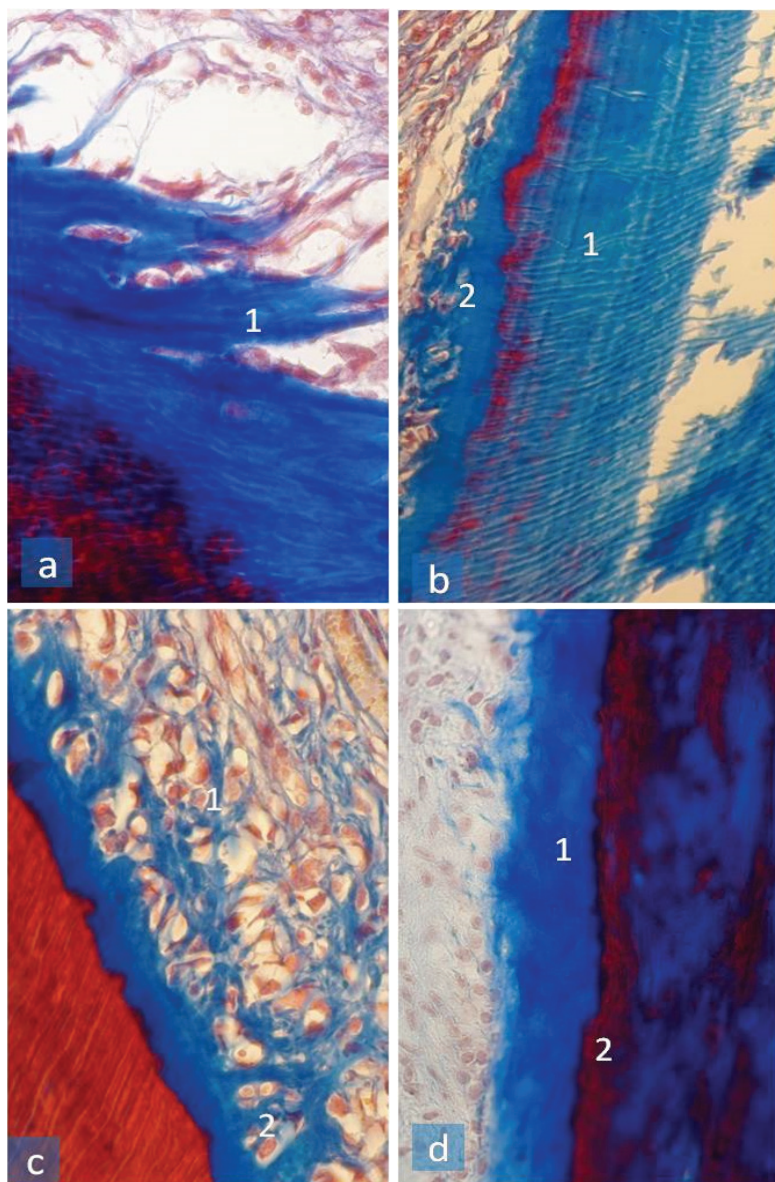


Fig. 2. Micro preparations. Histological sections of dental pulp biopsies of experimental animals of control (a, b) and main groups (c, d) on day 90 after the beginning of the experiment: a – coarse network of APhF in the central layers of the pulp (1); b – longitudinal (1) and circular (2) arrangement of APhF; c – thin APhF (1), single thickened and straightened Korff fibers (2); d – well-developed vascular pulp network, partially straightened APhF (1), passing into the dark strip – Fleischmann film (2) on the border between predentin, pulp and dentinal tubules. Masson color (a, b), silver impregnation by the Bilshovsky-Gross method (c, d). Ok. 20, Obj. 20

areas with petrification (deposition of calcium salts) in the dentinal tubules and odontoblast bodies. The tubules were strongly twisted and enlarged; at the initiation of their formation, many dichotomously divided and lost their structural anatomical structure.

Recent studies have shown a significant role of endothelium in the pathogenesis of various diseases. Notably, the endothelium synthesizes biologically active substances in large quantities, which play a crucial role in both healthy and pathological processes in the body (hemodynamics, homeostasis, immune reaction, and regeneration) [6, 7]. Damage to the endothelium has an important role in the pathogenesis of a variety of systemic pathologies (e.g., hypoxia, metabolic disorders, and atherosclerosis), because it initiates blood coagulation and blood vessel spasm after injury. Structural and functional studies of the endothelium have revealed its crucial role in the pathogenesis of PD [4, 8]. Biologically active endothelial cells participate in various mechanisms of homeostasis, including local circulation mechanisms. Endothelial activity typically provides trophic organs and plays a protective function, with highly integrated and self-regulating mechanisms entering the endothelium.

Conclusions. Modeling of pathological conditions in the tissues of periodontal and dental pulp on experimental animals enables prediction of changes in the dentoalveolar system in humans upon a significant increase in life expectancy [10, 11]. PD and OP, which accompany the aging problem, contribute to reduced quality of life and require changes in medical care for such patients. As evidenced in our study, the endothelium of the capillaries of the gingiva of the lower and upper jaw in PD is heterogeneous and reacts differently to antigen and subsequent changes in the composition of biologically active substances; these cause changes in the endothelial circle, as well as in pericytes, accompanied by a complex vascular-tissue reaction of the microcirculatory bed of periodontal tissues with a violation of the rheological properties of the blood, the formation of exudate, and an inflammatory cellular infiltrate. These results allow us to consider the use of drugs, biologically active substances, or techniques that ensure the integrity of the vascular endothelium, which is an obligatory component for such patients [12, 13].

Delayed changes in the pulpal state of the teeth and vascular bed in the experimental OP allow the development of both treatment methods and prevention methods with long-term effects. Beginning at 6 months to 1 year of OP modeling, the primary burden on the vascular network is associated with metabolic disturbances and changes in the argyrophilic pulpal system of the teeth. Thus, these circumstances encourage wider use of pharmacologic approaches for observation of elderly patients.

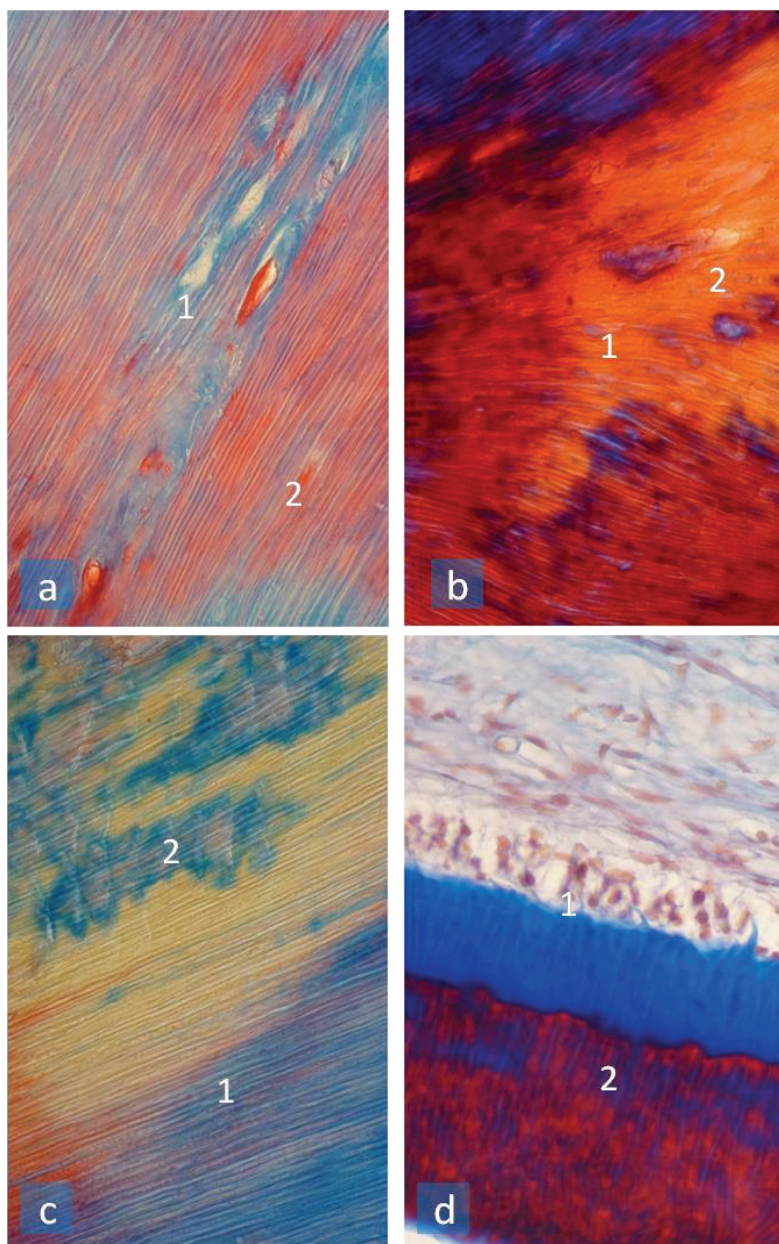


Fig. 3. Micro preparations. Histological sections of dental pulp biopsies of experimental animals of the main group at 180 (a, b) days and 1 year (c, d) after the beginning of the experiment: a – a dense shallow network of APbF resembling a mosquito net (1), lamination of cloak dentin in the form of dark lines running along its entire surface (Ebner's tangential fibers) (2); b – the pretense of the root part of the tooth (1), the formation of false parietal denticles (2); c – thin, poorly impregnated fibers of Korff (1); d – against the background of a complete absence of APbF (1), areas where petrification occurs in the dentinal tubules and in the sites of the odontoblast bodies (2) are noted. Masson color (a, c, d), silver impregnation according to Foot (b). Ok. 10, Obj. 20 (a, c, d); Ok. 20, Obj. 40 (b)

Disclosures:

The authors declare no conflict of interest.

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CHANGES IN STATE OF THE THIOL LINKAGES OF AN ANTIOXIDANT SYSTEM DURING ISCHEMIA AND REPERFUSION, AGAINST A BACKGROUND OF VASCULAR EXCLUSION IN THE RAT LIVER

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ИЗМЕНЕНИЯ СОСТОЯНИЯ ТИОЛОВОГО ЗВЕНА АНТИОКСИДАНТНОЙ СИСТЕМЫ В ИШЕМИЧЕСКИЙ И РАННИЙ РЕПЕРФУЗИОННЫЙ ПЕРИОДЫ ПРИ ВАСКУЛЯРНОЙ ЭКСКЛЮЗИИ ПЕЧЕНИ КРЫС

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The dynamic activities of glutathione reductase (GR) and glutathione peroxidase (GPO), as well as the concentration of reduced glutathione (GSH), were examined at both the organ and systemic levels in a liver ischemia-reperfusion model. Samples were collected at 5 min intervals from rats (n=95) during a 20 min ischemic