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CHANGES IN THE PHENOTYPE OF VASCULAR WALL CELLS IN CEREBROVASCULAR ATHEROSCLEROSIS IN PATIENTS WITH ISCHEMIC STROKE

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Nowadays, there is a lot of experimental and clinical evidence that atherosclerosis is a chronic inflammatory disease with an autoimmune component. Endothelial damage causes a cascade of inflammatory reactions involving monocytes, macrophages, T-lymphocytes, and vascular smooth muscle cells. In recent years, the pathogenesis of atherosclerosis has been associated with monoclonal proliferation of smooth muscle cells. The article studies the brain arteries' smooth muscle cells of the vascular walls in atherosclerosis in patients with ischemic stroke. It was determined that when cerebral vessels are damaged by atherosclerosis, there are subpopulations of smooth muscle cells in the vascular wall, which are characterized by the expression of desmin; smooth muscle cells are able to change their phenotype from contractile to synthetic, and this particular change in phenotype is one of the key points in the pathogenesis of atherosclerosis. This change of smooth muscle cells' phenotype in the endarterium activates proliferation and active synthesis of the connective tissue matrix components, i. e. the modified smooth muscle cells are responsible for the fibrous plaque insula formation.

Key words: smooth muscle cells of vascular wall, immune response, atherosclerotic plaques

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ЗМІНИ ФЕНОТИПУ КЛІТИН СУДИННОЇ СТІНКИ ПРИ АТЕРОСКЛЕРОЗІ СУДИН ГОЛОВНОГО МОЗКУ У ПАЦІЄНТІВ З ІШЕМІЧНИМ ІНСУЛЬТОМ

Зараз є багато експериментальних та клінічних доказів того, що атеросклероз є хронічним запальним захворюванням з аутоімунним компонентом. Ушкодження ендотелію викликає каскад запальних реакцій, у якому беруть участь моноцити, макрофаги, Т-лімфоцити та клітини гладких м'язів судин. В останні роки патогенез атеросклерозу повязують з моноклональною проліферацією гладком'язових клітин. У статті досліджуються гладком'язові клітини стінок артерій головного мозку при атеросклерозі у пацієнтів з ішемічним інсультом. Визначено, що при ураженні судин головного мозку атеросклерозом в стінці присутні субпопуляції гладком'язових клітин, для яких характерна експресія десміну, гладком'язові клітини здатні змінювати свій фенотип із скоротливого на синтетичний і ця зміна фенотипу є одним із ключових моментів патогенезу атеросклерозу. Дана зміна фенотипу гладком'язових клітин внутрішньої оболонки артерій викликає активізацію проліферації і активний синтез компонентів сполучнотканинного матриксу, тобто модифіковані гладком'язові клітини відповідають за формування фіброзного остова бляшок.

Ключові слова: гладком'язові клітини судинної стінки, імунна відповідь, атеросклеротична бляшка.

The study is a fragment of the research project "Improving prevention, treatment and rehabilitation of patients with hypertension and coronary heart disease with comorbid pathology in outpatient and inpatient settings", state registration No. 0117U002120.

Vascular atherosclerosis is the most common pathology of coronary heart disease, peripheral artery disease and cerebrovascular disease [4]. Multifactorial impacts, including aging, gender, smoking, diabetes, dyslipidemia, hypertension, and genetic factors, have been proven to be involved in atherosclerotic disease, but the etiology of atherosclerosis remains unknown. Many studies confirm the role of inflammation and immunity in the development of atherosclerosis [6, 10].

Chronic accumulation of plaque that blocks blood vessels in the subendothelial layer (Langhans layer) in the intima of large and medium arteries consequentially leads to significant stenosis, resulting in limited blood flow and critical tissue hypoxia [8]. The most common complications of vascular atherosclerosis are myocardial infarction and cerebral ischemic stroke, caused by spontaneous occlusion of thrombotic vessels being the most common cause of death worldwide [7,9]. A large number of reliable data obtained from animal experiments, observations of human atheromas and clinical studies of biomarkers confirm the importance of immune and inflammatory pathways in the pathogenesis of this disease. For most of the 20th century, research focused on cholesterol and later – on lipoproteins as a key mechanism of fatty damage formation in the arteries [8]. Although low-density lipoprotein (LDL) promotes atherothrombosis, other lipoprotein fractions, non-lipid-related genetic predisposition, and lifestyle also influence the disease [12]. Almost half of the population can hide subclinical atherosclerosis without the presence of traditional risk factors [3]. Therefore, elevated LDL levels alone cannot indicate atherosclerosis.

The concept of atherosclerosis as a proliferative disorder of arterial smooth muscle cells has gained popularity as a pathogenic pathway independent of cholesterol. In recent years, the occurrence and development of atherosclerosis is considered from the standpoint of smooth muscle cells' (SMC) monoclonal proliferation and immune inflammation, where the role of immunocompetent cells is important [13]. Chemical, mechanical or immunological damage to the endothelium, followed by platelet deposition and the release of platelet-derived protein growth factor, received by thrombocytes, stimulates the migration and proliferation of smooth muscle cells. [1]. In a series of experimental studies, it was found that SMCs of the vascular wall can change their phenotype from contractile to synthetic, with the rearrangement of cells' ultrastructural components in which the expression of proteins, such as vimentin, actin and desmin, changes. Adhesion of monocytes on the luminal surface of arteries, presence of a large number of these cells under the endothelium, and more mature macrophages in the depths of the intima, indicates the entry of these cells from the blood into the artery wall [15]. Thus, atherosclerosis is a chronic inflammatory disease with an autoimmune component [2]. In vascular atherosclerotic plaques, SMCs are found which actively express antigens of T-lymphocytes' proteins, namely the main complex of class II histocompatibility. It indicates the ability of SMCs to participate in immune responses in atherosclerosis [14].

The purpose of the work was to study the ability of vascular wall's smooth muscle cells to change their phenotype and their involvement in immune responses in cerebrovascular atherosclerosis.

Materials and methods. The study was performed on 50 deceased individuals with atherosclerosis of cerebral vessels, 50 deceased with cerebral vessels atherosclerosis without ischemic stroke and 20 deceased from causes not related to atherosclerosis (comparison group).

Arteries of the same structural and functional level were under study: extracerebral – arteries in the base of the brain, where 2–3 segments were taken from the infarct area, with lipid and fibrous plaques, in the comparison group – unchanged areas. Histological tissue specimens were stained with hematoxylin-eosin, trichrome according to Masson, and immunohistochemical examination was also performed using markers CD4 (CD4 Ab–8), CD8 (SP–16), CD20 (CD20 Ab–1), CD68 (CD68/Macrophage Marker Ab–4), Actin Smooth Muscle Ab–1 (Clone 1A4); Desmin (Muscle Cell Marker Ab–1 Clone D33); Vimentin Ab–2 (Clone V9).

The material was fixed in a 10 % solution of neutral buffered formalin, performed according to conventional procedure. For immunohistochemical reactions, sections 4–5 μm thick were mounted on Super Frost Plus adhesive slides (produced by Menzel), dewaxed, hydrated, and treated with 3 % hydrogen peroxide solution to block endogenous peroxidase. The Ultra Detection System kit (produced by Thermo Scientific) was used for other antibodies. To separate nonspecific structures, sections were additionally stained with Mayer's hematoxylin.

Results of immunohistochemical reactions of CD4 markers (CD4 Ab–8) –marker of T–helpers, CB8 (SP 16) – marker of T–suppressors, CD20 (CD20 Ab–1) –marker of B–lymphocytes and CD68 (CD68/Macrophage Marker Ab–4) were assessed by counting cells with a positive color in 10 randomly selected microscope fields of view at magnification of 400. In addition, the color intensity degree was assessed: 0 – no color, 1 (+) – weak – light brown color, 2 (++) – moderate – brown color, 3 (+++) – pronounced – dark brown color.

Actin Smooth Muscle Ab–1 (Clone 1A4), Desmin (Muscle Cell Marker) Ab–1 (Clone D33); Vimentin Ab-2 (Clone V9) were used to determine mesenchymal cells and their derivatives – endothelial cells, smooth myocytes, fibroblasts, pericytes; the result was estimated as the specific volume of immunopositive cells per area unit. The results of the immunohistochemical reaction were assessed by a semi-quantitative method in points from 0 to 6 according to the conventional procedure, taking into account the stained cells. 0 points were determined in the absence of color, 1 point – up to 10 %, 2 points – up to 20 %, 3 points – up to 30 %, 4 points – up to 40 %, 5 points – up to 50 %, 6 points – more than 50 % of the stained cells. In addition, the color intensity degree was assessed: 0 – no color, 1 (+) – weak – light brown color, 2 (++) – moderate – brown color, 3 (+++) – pronounced – dark brown color.

Histological examination and photography of microslides were performed with an AxioScop 40 microscope (Zeiss, Germany). Data of morphometric studies were subjected to statistical processing with a personal computer using the standard Microsoft Excel software, the results were processed by the method of variation statistics and considered reliable at $p<0.05$ (p–level of significance).

Results of the study and their discussion. Manifestations in the form of lipid spots, fibrous plaques, calcification, stenosis, and obliteration were observed in the studied groups with manifestations of atherosclerosis. The decrease in vascular lumen was mainly due to muscular-elastic or muscular-fibro-elastic hyperplasia of the internal membrane of cerebral arteries and carotid arteries.

The most pronounced changes are observed in the areas of blood vessels' functional load – bifurcation of arteries. The predominance of stenotic and obliterating variants of vascular impairment was noted, with internal membrane hyperplasia and diffuse-focal lymphocytic-macrophage infiltration.

Inflammatory cell infiltration, especially accumulation of macrophages, is a major factor stimulating plaque activity. Special staining, targeted at macrophages or lymphocytes, is a direct and acute method of assessing the involvement of inflammation in atherosclerotic plaques (fig. 1).

Macrophages with lipid inclusions, so-called xanthoma cells, with foamy cytoplasm and round nucleus were observed in the areas of intima proliferation.

Atherosclerotic plaques consist of cells, connective tissue extracellular matrix and intracellular and extracellular lipid deposits. The proportion of these three components differs in different atherosclerotic plaques, and this affects the stability of plaques and causes a wide range of lesions:

1) the so-called fatty streaks are characterized by the adhesion of monocytes to the endothelium and migration to the subendothelial arterial wall layer in adolescents and young adults;

2) with age, fatty streaks turn into fibrous plaques, consisting of the nucleus of cell residues, free extracellular lipid and cholesterol crystals under the "cap" of foam cells, transformed smooth muscle cells, lymphocytes and connective tissue;

3) the most advanced stage of atherosclerosis is a complicated impairment, which includes calcification, hemosiderin deposition and disturbance of the lumen surface.

In most arteries, wall thickening was associated with the proliferation of connective tissue fibers, mainly collagenous (fig. 2).

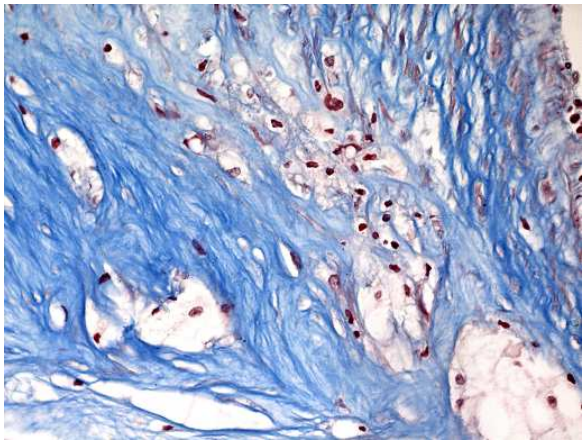

Fig. 1. Atherosclerotic plaque in the artery wall, macrophages with lipid inclusions. Masson's Trichrome staining. x200.

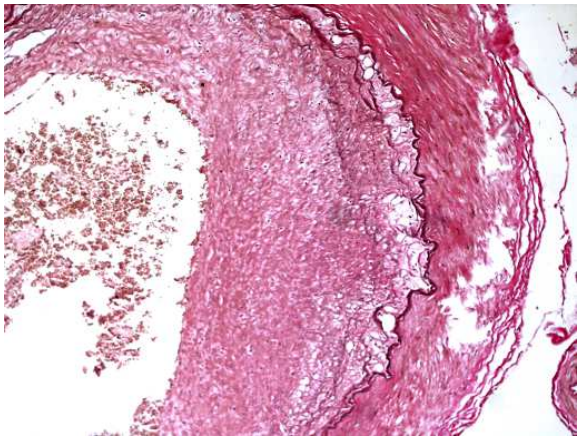

Fig. 2. Thickening of the artery wall due to proliferation of collagen fibers. Staining: picrofuxin according to Van Gieson, resorcinol-fuchsin according to Weigert x200.

The proliferation of collagenous fibers led to a thickening of the inner layer of arteries, which caused a significant narrowing of their lumen. In many cases, the presence of homogeneous eosinophilic masses and their clear boundary with the preserved tissue, macrophage reaction and proliferation of fibroblasts was observed.

Development of atherosclerotic lesions was characterized by migration of smooth muscle cells into the intima and their proliferation. After migration into the intima and proliferation, smooth muscle cells probably produced collagen and elastin, i.e. the connective tissue base for atherosclerotic plaque. In all atherosclerotic plaques there were areas of fibrosis that surrounded the lipid focus in the form of a capsule and consisted mainly of collagen fibers, among which elastic fibers and a large number of fibroblasts were found. Atherosclerotic plaques protrude into the lumen of blood vessels, creating an obstacle to blood flow.

Smooth muscle cells that migrated to the intima from the middle membrane transformed into secretory cells, intensively producing connective tissue proteins with elastin and collagen. Subsequently, fibrous tissue was formed, which surrounded the lipid focus in the form of a capsule. Smooth muscle cells that migrated to the intima from the middle membrane of the arteries became metabolically active, despite the absence of scavenger receptors, they intensively absorb modified lipoproteins, i. e. they also formed foam cells.

Immunomorphological analysis of the arterial walls showed that with the exception of the endothelium, all cells of the intima and media react with antibodies to vimentin (fig. 3).

In immunohistochemical reaction with vimentin the presence of connective tissue components, and also the expressed fibrosis of an artery wall were observed. Fibrous plaques acquired different sizes and shapes, from small segmental to circular, and sometimes multiple, which led to the vessel sclerosing in large areas.

In the study of arterial wall vimentin in a group of patients with ischemic stroke, its expression was 59.6±4.8 % ($p>0.05$) compared to the total area. In the comparison group, the expression of vimentin was 54.2±6.4 ($p>0.05$), in the group with cerebral vessels atherosclerosis without ischemic stroke – 56.3±5.1 ($p>0.05$), so there is no significant differences.

In many cases, the formation of longitudinal folds of the vessel wall, protruding into the lumen of the vessel and narrowing it by half, changes were observed in the muscle layer, the muscle layer was sharply thickened with delamination and high expression of vimentin. There was a sharp tortuosity of the inner elastic membrane.

Expression of vimentin showed that fibrosis of the vascular wall increases with the progression of atherosclerotic plaque.

In addition, all media and intima cells reacted with antibodies to alpha actin. The expression of alpha-actin in the group with ischemic stroke was 62.8±7.6 % (p>0.05).

In the comparison group, the expression was 55.7±5.2 % (p>0.05); in the group with cerebral vessels atherosclerosis without ischemic stroke – 60.3±8.7 % (p>0.05).

Changes in the inner elastic membrane were manifested in delamination, sometimes to its complete disappearance, which probably led to the penetration of lipids into the middle membrane, as well as defibering and increased tortuosity.

Desmin expression, in many cases, was diffuse in nature, with a clear boundary line with the surrounding tissues. Proliferation of smooth muscle cells and hyperproduction of connective tissue fibers were noted, this explains the reason for the intima thickening with the subsequent formation of fibrous plaque. Desmin expression was not found in intima cells, but was only detected in part of the media SMCs.

Quantitatively, in the group of patients with ischemic stroke, the expression of desmin was 14.6±3.4 % (p>0.05) compared to the total area.

Therefore, in ischemic stroke in the arterial wall in the media there is a significantly higher expression of desmin in the SMC compared to the control group.

Activation of smooth muscle cell proliferation in the intima of blood vessels, migration of myocytes from the middle membrane and increase in their number depends on fibroblast and endothelial factors. The synthesis of connective tissue matrix components was also detected, i.e. collagen and elastin, which subsequently led to thickening of the intima and to the formation of fibrous plaque.

Adhesion of monocytes on the arteries' luminal surface, a large number of monocytes under the endothelium, and more mature macrophages in the depth of the intima were observed, which indicates the entry of these cells into the arterial wall from the blood.

In the areas of atherosclerotic lesions, a significant amount of CD68-positive cells with marker expression in the cytoplasm was observed (fig. 4), which made 16.68±1.82 (p>0.05) in the group with ischemic stroke.

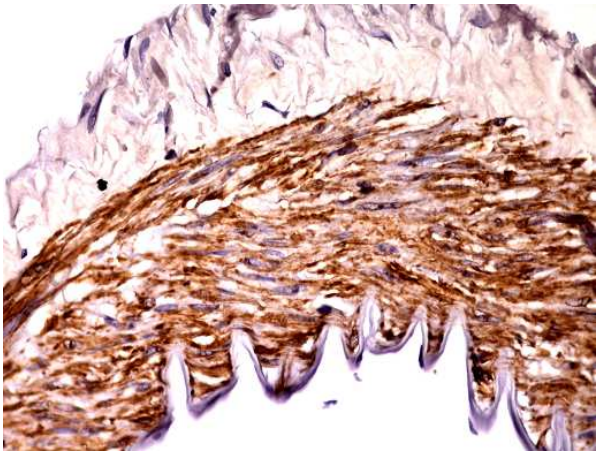

Fig. 3. Intense expression of the Vimentin Ab-2 marker in the artery wall. Staining: immunohistochemical technique with primary Vimentin Ab-2 antibodies of positive cells. x200.

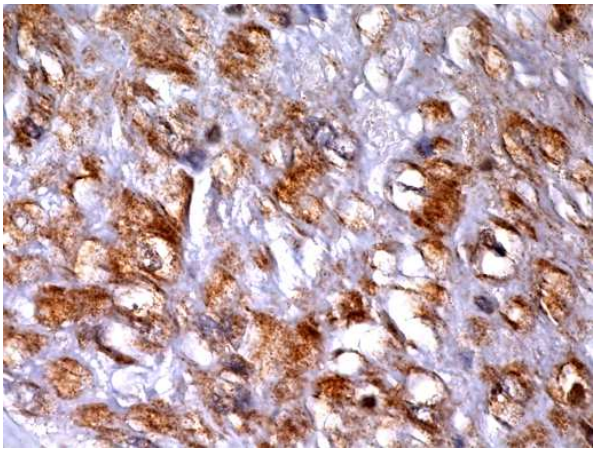

Fig. 4. Intense expression of the CD68 marker in the artery wall of a patient with ischemic stroke. Staining: immunohistochemical technique with primary antibodies of CD68 positive cells. x400.

In the group with cerebrovascular atherosclerosis without ischemic stroke, the number of CD68 positive cells with marker expression in the cytoplasm was 7.34±1.73 (p>0.05).

Local infiltration by macrophages in the areas of atherosclerotic lesions was frequently combined with accumulation of T-lymphocytes, which indicates the inflammatory nature of the process.

Helper T-lymphocytes (CD4, membrane expression) in the areas of atherosclerotic lesions formation made 11.18±1.76 (p>0.05) in the group with ischemic stroke and 10.32±1.24 (p>0.05) in the group with atherosclerosis of the cerebral vessels without ischemic stroke (p> 0.05). T-lymphocyte suppressors (CD8, membrane expression) were 8.56±1.16 (p>0.05) and 9.12±1.64 (p>0.05), respectively

Accumulation of blood monocytes in the damaged layer of endothelium and subendothelial space was noted, with their subsequent transformation into macrophages, lipid uptake, the cytoplasm acquired a foamy look, i.e. foam cells were formed.

B-lymphocytes (expression –, membrane, cytoplasm) were present in smaller numbers – 5.34±0.86 ($p>0.05$) in the area of atherosclerotic lesions in ischemic stroke and 6.04±1.14 ($p>0.05$) with cerebral vessels atherosclerosis without ischemic stroke. In areas of atherosclerotic lesions in hemorrhagic stroke, there was a tendency to increase the number of positively stained cells. Cells with suppressor functions singly or in small groups were present among the endothelial cells of the microcirculatory bed.

Local infiltration by macrophages in the areas of atherosclerotic lesions is frequently combined with the accumulation of T-lymphocytes, which indicates the inflammatory nature of the process [15].

It has been found that both congenital (macrophage) and acquired (T cells and other lymphocytes) immune response cells contribute to the development of atherosclerosis.

Inflammation begins when endothelial cells are activated and secrete adhesion molecules, and smooth muscle cells secrete chemokines and chemoattractants, which together draw monocytes, lymphocytes, mast cells, and neutrophils into the arterial wall. Smooth muscle cells of the intima also secrete proteoglycans, collagen, and elastic fibers into the extracellular matrix [5]. The immune response in atherosclerotic lesions was represented by cellular and humoral links, i. e. cellular link was provided by T-helpers and cytotoxic T-lymphocytes, and humoral link – by B-lymphocytes that produce immunoglobulins.

A number of studies have shown that in atherosclerotic plaques of vessels smooth muscle cells were revealed that actively express antigens of the main histocompatibility class II complex, which provides evidence of T-lymphocytes' functional activity in the arterial plaque. These activation proteins are characteristic of T lymphocytes and macrophages and are involved in the receptor transmission of immune information, which indicates the ability of SMC to participate in immune responses in atherosclerosis [11].

Conclusion

In the arterial wall there are subpopulations of SMCs, which are characterized by the expression of desmin and vimentin, so SMCs are able to change their phenotype from contractile to synthetic, and this change in the SMCs phenotype is one of the key moments in the pathogenesis of atherosclerosis. In atherosclerotic lesions of the cerebral arteries, immunocompetent cells – macrophages and lymphocytes – play a significant role in the morphogenesis of changes in the vascular wall with the formation of atherosclerotic plaques, as evidenced by their accumulation in areas of atherosclerotic lesions in the arteries. Macrophages in the vascular wall due to the accumulation of lipids are transformed into foam cells, and lymphocytes due to the cellular and humoral immune response potentiate further formation of atheromatous plaque.

Inflammation begins when endothelial cells are activated and secrete adhesion molecules, and smooth muscle cells secrete chemokines and chemoattractants, which together draw monocytes, lymphocytes, mast cells, and neutrophils into the arterial wall. Smooth muscle cells of the intima also secrete proteoglycans, collagen, and elastic fibers into the extracellular matrix.

Therefore, the obtained data indicate that the change in the SMC phenotype of the arterial intima is accompanied by increased proliferation and synthesis of collagen, and modified SMCs, with their high activity in proliferation and synthesis of connective tissue matrix components, are responsible for the formation of fibrous plaque.

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INCREASING THE EFFICIENCY OF TREATMENT OF INFLAMMATORY PERIODONTAL DISEASES IN PATIENTS WITH THYROID DISEASES

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A comprehensive periodontal examination and questionnaire survey of 150 people suffering from thyroid dysfunction and chronic generalized periodontitis (the average age of patients was 31.6±0.46 years) and 150 practically healthy persons of the same age and sex were carried out. The level of MDA concentration after completion of the course of basic therapy in all groups was 0.71±0.03 nmol/ml, 1.30±0.03 nmol/ml, and 2.89±0.15 nmol/ml, respectively, in the main group. the control group and the comparison group. The results of biochemical studies showed a less pronounced trend in comparison with the main group of patients in the normalization of the content of S-IgA immunoglobulins – 0.46±0.023 mg/l. The fact of a more pronounced increase in the amount of sIgA in saliva after the use of hyaluronic acid is associated with a significant activation of immunological processes in the oral cavity.

Key words: periodontal disease, hypothyroidism, saliva, immunity, antioxidant system, hyaluronic acid

Ш.Р. Юсубова, Ф.Ю. Мамедов

ПІДВИЩЕННЯ ЕФЕКТИВНОСТІ ЛІКУВАННЯ ЗАПАЛЬНИХ ЗАХВОРЮВАНЬ ПАРОДОНТА У ПАЦІЄНТІВ ІЗ ЗАХВОРЮВАННЯМИ ЩИТОПОДІБНОЇ ЗАЛОЗИ

Проведено комплексне пародонтологічне обстеження і анкетування 150 осіб, які страждають порушеннями функції щитоподібної залози і хворіють на хронічний генералізований пародонтит (середній вік пацієнтів склав 31,6±0,46 років) і 150 практично здорових осіб аналогічного віку та статі. Рівень концентрації МДА після завершення курсу базової терапії у всіх групах дорівнював 0,71±0,03 нмоль/мл, 1,30±0,03 нмоль/мл і 2,89±0,15 нмоль/мл, відповідно до основної, контрольній групі і групи порівняння. Результати біохімічних досліджень показали менш виражену в порівнянні з основною групою пацієнтів тенденцію до нормалізації вмісту імуноглобулінів S-IgA - 0,46±0,023 мг/л. Факт більш вираженого збільшення в слині кількості sIgA після застосування гіалуронової кислоти пов'язаний зі значною активізацією імунологічних процесів в порожнині рота.

Ключові слова: захворювання пародонту, гіпотиреоз, слина, імунітет, антиоксидантна система, гіалуронова кислота

The work is a fragment of the doctoral thesis: "Role of general somatic diseases in increasing the prevalence and intensity of major dental diseases and improvement of treatment and prophylactic measures"

The modern concept of the etiology and pathogenesis of dental diseases considers the systemic-somatic risk factor as one of the leading among a rather extensive complex of mechanisms that determine the development of pathological processes of an inflammatory and destructive nature in the organs and tissues of the oral cavity [1].

In the course of scientific research, some etiopathogenetic aspects of periodontal diseases of an inflammatory and destructive nature and dental caries were identified and, ultimately, a close relationship and interdependence of diseases of the oral cavity with endocrine pathologies was determined [2]. A number of systemic immune disorders and the destructive effect of free radicals, including at the local level, with a lack of thyroid hormones, which have immunostimulating and corrective properties, have also