AZERBAIJAN REPUBLIC

On the rights of the manuscript

ENDOTHELIAL DYSFUNCTION AND MECHANISMS OF TISSUE LYMPHATIC DRAINAGE IMPAIRMENT IN THE PATHOGENESIS OF MULTIPLE ORGAN FAILURE IN DIABETES MELLITUS

Spesiality: 3205.01- Internal Medicine
3243.01 - Pathological physiology

Field of science: Medicine

Applicant: **Aytan Yagub Mammadzada**

ABSTRACT

for the degree of Doctor of Science

Baku – 2024

The dissertation work was carried out at the Department of Pathological Physiology, Department of Internal Medicine I and the Educational and Therapeutic Clinic of the Azerbaijan Medical University

Scientific consultant: Doctor of Medical sciences, professor **Yagub Ziyaddin Gurbanov**

Scientific consultant: Honored Scientist, Doctor of Medical sciences, professor **Sabir Jahan Aliyev**

Official opponents:

Doctor of Medical sciences, professor **Tamfira Tamerlan Aliyeva**

Doctor of Medical sciences, professor **Faig Gadir Islamzada**

Doctor of Medical sciences, docent **Eldar Mursal Hatamzada**

Doctor of Medical sciences **Rashad Farhad Sholan**

Dissertation Council BED 2.27/1 of Supreme Attestation Commission under the President of the Republic of Azerbaijan operating at the Azerbaijan Medical University

Chairman of the Dissertation council:

Doctor of Medical sciences, professor **Vasadat Ali Azizov**

Scientific secretary of the Dissertation council:

Doctor of Philosophy in Medicine, Associate Professor **Tora Akif Sadigova**

Chairman of the scientific seminar:

Doctor of Medical sciences, professor **Alihuseyn Alishan Hidayatov**

İMZANI TƏSDİQ EDİRƏM
Azərbaycan Tibb Universitetinin
ELMİ KATİBİ
Tibb elmləri doktoru, professor
Nazim Adil oğlu Pənahov
01.04.2024

GENERAL CHARACTERISTICS OF THE RESEARCH

Relevance of the research: Today, diabetes mellitus (DM) ranks third in the structure of mortality in adults after cardiovascular diseases and cancer. Due to population growth, an increase in the number of people with obesity and a sedentary lifestyle, the number of patients with diabetes in the world is steadily increasing. According to the International Diabetes Federation, the number of people with diabetes among the adult population (20-79 years) in the world today is 537 million[1].

Along with the steady increase in morbidity, disability is also rapidly increasing due to serious complications of the pathology. Statistics show that every 10-15 years the number of people with diabetes doubles. The social significance of this disease is primarily due to changes in the quality of life of patients with diabetes. Regardless of what type of disease the patient has, the patient must, in order to maintain a normal level and quality of life, develop the necessary qualities, such as resistance to stress, discipline, and responsibility. In addition, he must have a sufficient level of knowledge about his disease and be able to control it[2].

The main problem of this disease is the occurrence and development of vascular complications. Depending on the size of the affected vessels, microvascular and macrovascular changes are distinguished. Macroangiopathies are classified according to localization and clinical development.

Diseases such as coronary heart disease, severe vascular lesions of the lower extremities, and cerebral vascular lesions are one of

1. IDF Diabetes Atlas 2021, 10th edition https://diabetesatlas.org/atlas/tenth-edition/ (Accessed on January 17, 2022,p.5)
2. Водолагин, Михаил Витальевич Оценка влияния медико-социальных факторов на приверженность пациентов с сахарным диабетом к модификации образа жизни. / Водолагин Михаил Витальевич, Эккерт Наталья Владимировна, & Козлов Василий Владимирович // Siberian Journal of Life Sciences and Agriculture – 2021. – 13 (5), –с.247-263.

the main causes of disability and mortality in patients with type 2 diabetes. 25% of macroangiopathies account for stroke and peripheral vascular damage, in the remaining 75% of cases it occurs as coronary heart disease[3].

It is known that in patients with type 2 diabetes, simultaneously with macroangiopathies, various forms of microangiopathies also occur and progress. Among them are pathologies such as renal lesions - nephropathy, vascular lesions of the eye - retinopathy, etc[4]. The duration of the underlying disease is directly proportional to the development of chronic vascular complications, aggravating the clinical course of the disease itself. ¼ of all patients with type 2 diabetes suffer from vascular damage to the kidneys and eyes; half of the patients have diabetic neuropathy. The duration of type 2 diabetes along with inadequate correction of glycemia, uncontrolled arterial hypertension (AH), and dyslipidemia is the main classic risk factor development of macro and microangiopathies and this is a consequence early development of endothelial dysfunction (ED). Before the appearance of atherosclerosis, the development of ED already occurs. And, ED, being an early manifestation of vascular complications, is considered an important prognostic marker.

Diabetic nephropathy (DN) is the most common microvascular complication in patients with diabetes[5]. Its frequency is about 30% in patients with type 1 diabetes and 40% in patients with type 2 diabetes. Changes in the renal microvasculature in patients with diabetes can cause diabetic nephropathy, characterized by damage to glomerular endothelial cells (GECs), thickening of the

---

3. WHO/NCD/NCS/99.2. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. World Health OrganizationDepartment of Noncommunicable Disease Surveillance Geneva; −1999.−65 p.
4. Hamid, M. Molecular mechanisms of disorders of lipid metabolism in chronic kidney disease / Hamid M., Nosratola D. Vaziri. // Frontiers In Bioscience, Landmark, −2018, − January 123, − p.146-161
5. Ighodaro O.M., Adeosun A.M. Vascular complications in diabetes mellitus. Glob J Endocrinol Metab. 2017;1(2):1–3

basement membrane, proliferation of the glomerular mesangial matrix and nodular glomerulosclerosis. Recent studies have shown that approximately 12–52% of cases of end-stage chronic kidney disease are associated with diabetes. The discovery of GECs and endothelial cells around the renal tubules has proven that they play a major role in basement membrane selectivity and quality urine filtration[6]. The GECs is formed by negatively charged complex glycocalyx molecules that form a network with glycosaminoglycans. As DN progresses in diabetic patients, a gradual decrease in fenestrated endothelial surface can be observed. In patients with T2DM, a decrease in glomerular endothelial pores is closely associated with reduction in proteinuria and glomerular filtration rate (GFR). Hyperglycemia and its by-products can promote the growth of pro-oxidants and induce a pro-inflammatory milieu with GEC dysfunction, leading to proteinuria and renal fibrosis. In DN, ED not only determines the rate of progression of nephrosclerosis, but also initiates structural and functional changes in the arterial bed to the clinical stage. Researchers have found that when renal function is impaired, generalized changes in the endothelium lead to a slowdown in the glomerular filtration rate, which, in turn, leads to hyperactivation of the RAAS[7]. Hyper- and dyslipidemia, hypertension, anemia, oxidative stress and other risk factors are a trigger for the processes of proapoptosis and vascular hypoxia-. The end products of glycation - EPGs and forms of active oxygen - FAO increase in diabetes, activate white blood cells and increase the transcription of

6. Reidy, K., Kang HM., Hostetter T., Susztak K. Molecular Mechanisms of Diabetic Kidney Disease. J Clin Invest (2014) 124:2333-40
7. Məmmədov, C.T., Xroniki böyrək çatmamazlıqlı xəstələrdə proqramlı hemodializ fonunda endotelial disfunksiyanın vəziyyəti / Məmmədov C.T., Quliyeva A.R. / Təbabətin aktual problemləri elmi-praktik konfransın materialları. Bakı: – 2017, –s.74

NF-κB in vascular endothelial cells[8, 9]. Research results have shown that, during hyperglycemia, NF-κB also increases the production of intracellular adhesion molecules-1 (IAM-1). A number of studies have shown that high levels of vascular adhesion molecule-1 (VAM-1) and IAM-1 expression during hyperglycemia are directly correlated with the occurrence and progression of diabetic nephropathy. According to the results of statistical data, kidney damage is directly related to the level of circulating VAM-1 and the concentration of IAM-1 in the blood. This explains the high level of these products in diabetic patients with nephropathy compared to patients without kidney damage. Proteinuria is one of the prognostic factors for kidney damage. However, circulating IAM-1 is also increased in proteinuria, making it an independent risk factor for kidney damage. While VAM-1 is responsible for the process of proteinuria, IAM-1 is directly associated with resistant and long-lasting microalbuminuria[10]. It has also been revealed that there is a multidirectional connection between IAM-1 and GECs, which plays a role in inflammatory processes in the kidneys, thereby ensuring the migration of T cells to the site of the lesion.

The leading role in the formation of ED in patients with diabetes is the accumulation of ROS and the synthesis of diacylglycerol, which leads to modulation of the activity of various nitric oxide synthase (eNOS)[11].

---

8. Chawla A, Chawla R, Jaggi S. Microvasular and Macrovascular Complications in Diabetes Mellitus: Distinct or Continuum? Indian J Endocrinol Metab – (2016) 20 (4): –546–51.
9. Whitehead, M, Wickremasinghe S, Osborne A, Van Wijngaarden P, Martin KR. Diabetic Retinopathy: A Complex Pathophysiology Requiring Novel Therapeutic Strategies. Expert Opin Biol Ther (2018) 18(12):1257–70.
10. Chawla A, Chawla R, Jaggi S. Microvasular and Macrovascular Complicatio s in Diabetes Mellitus: Distinct or Continuum? Indian J Endocrinol Metab – (2016) 20 (4): –546–51.
11. Nellaiappan K, Preeti K, Khatri DK, Singh SB. Diabetic Complications: An Update on Pathobiology and Therapeutic Strategies. Curr Diabetes Rev (2022) 18(1):e030821192146

This alters nitric oxide (NO) production through eNOS expression, directly affects vascular tone and permeability, and ultimately contributes to endothelial dysfunction. During the pathogenesis of DN, AT-II causes vasoconstriction, inflammation, oxidative stress, cellular dysfunction, angiogenesis and fibrosis, thereby increasing ROS production and directly damaging endothelial cells.

Advanced glycation end products are considered free atherogenic factors. They lead to increased endothelial permeability, increased adhesion of blood cells, and proliferation of muscle cells. The formation of ED in patients with diabetes is associated with the accumulation of end products of protein glycation in the subendothelial areas and the activation of free radicals, accompanied by an increase in superoxide anions, which, in turn, oxidize low-density lipoprotein (LDL)[12, 13].

As LDL passes through the endothelium, it is oxidized, and more peroxidized and modified atherogenic LDL passes through the intima.

By interacting with coagulation factors, they activate the expression of molecules that control thrombus formation, as well as the plasminogen activation inhibitor by accelerating the process of monocyte sedimentation on damaged areas of the endothelium. Considering the above pathogenetic links of DM, it is very relevant to study ED indicators in relation to indicators of lipid metabolism, lipid peroxidation (LPO) activity and the antioxidant system in the blood and cells of visceral organs.

It should be noted that until today, when studying the pathogenesis of diabetic angiopathy, the circulatory system was mainly studied, while the lymphatic system remained outside the field of view of scientists. There is enough data in the literature indicating that the lymphatic system, being a system of endothelial tubes (capillaries and vessels) penetrating most organs, is involved in all pathological

12. Dıaz-Cora´´nguez M, Ramos C, Antonetti DA. The Inner Blood-Retinal Barrier: Cellular Basis and Development. Vision Res (2017) 139:123–37

13. Gorus, F.K. Selective uptake of alloxan by pancreatic B-cells / F.K. Gorus, W.J. Malaisse, D.G. Pipeleers // Biochem J. – 1982. – V. 208. – p. 513-515.

processes and at the same time changes occur in the system of coagulation, anticoagulation and fibrinolysis (CAF) not only in the blood, but also in the lymph[14, 15].

Moreover, isolated data available in the literature indicate the active involvement of the lymphatic system in the pathogenesis of various complications of diabetes and a significant increase in the therapeutic effect when lymphotropic drugs are included in the complex of glucose-lowering therapy. However, to date, disturbances in the morphofunctional state of endothelial cells of the lymphatic system, the SAF system and the lipid composition of lymph, and their role in the pathogenesis of disorders of lymphatic tissue drainage during the development of vascular complications in diabetes remain unexplored.

All of the above facts arouse great interest in the study of ED in diabetes with the aim of studying the subtle pathogenetic mechanisms of diabetic vascular complications of various organs, developing new approaches to early diagnosis, prevention and treatment. There is evidence that, along with the elimination of classical risk factors for atherosclerotic changes in blood vessels, it is necessary to develop a correction for ED. And this should be considered as a new direction in the effective prevention of macro and micro angiopathy in diabetes.

The object of the study: "Chinchilla" breed rabbits and people with diabetic nephropathy

The aim of study is to study ED in the pathogenetic relationship with disorders of LPO, cytokine status, liver enzyme activity, the CAF system and the composition of lipids in the circulatory and lymphatic links with vascular complications against the background of experimental diabetes, as well as to study ED in patients with diabetic nephropathy with the development correction methods.

---

14. Hayes, JD, Flanagan JU, Jowsey IR. Glutathione transferases. Annu Rev PharmacolToxicol. 2005; 45 (1),-p. 51−88.
15. Черных, В.В. Роль лимфатической системы в увеосклеральном оттоке внутриглазной жидкости / Черных В.В., Бородин Ю.И., Бгатова Н.П. [и др.] // Офтальмохирургия. − 2015; − 2: − 4-79.

Objectives of the study:

1. To study markers of ED, LPO, cytokine profile, liver enzyme activity, CAF system and lipid composition in the blood and lymph when modeling diabetes.
2. To study the relationship between indicators of ED, LPO, cytokine profile, liver enzyme activity, CAF system and lipid composition in the blood and lymph against the background of experimental diabetes.
3. To study indicators of ED, LPO, cytokine profile, liver enzyme activity, CAF system and lipid composition in the blood and lymph, as well as the state of lymphatic drainage of tissues when modeling myocardial infarction against the background of experimental diabetes.
4. To study indicators of ED, LPO, cytokine profile, liver enzyme activity, CAF system and lipid composition in the blood and lymph when modeling occlusion of the artery of the lower limb and the renal artery against the background of experimental diabetes.
5. To study the relationship between lymphatic tissue drainage and ED indicators when modeling various vascular complications of diabetes.
6. To study indicators of ED, LPO, cytokine profile, liver enzyme activity, CAF system and lipid composition in the blood and lymph when modeling renal artery occlusion against the background of experimental diabetes under the influence of glycyram.
7. To study the relationship between the functional state of the kidneys and markers of endothelial damage in patients with different stages of DN;
8. Determine indicators of ED, lipid composition, cytokine profile in the blood, as well as endothelium-dependent and independent vasodilation of the brachial artery (BA) at various stages of DN and their relationship.
9. To study indicators of ED, lipid composition and functional state of the kidneys in patients with diabetic nephropathy when glycyram is included in the complex of generally accepted basic therapy.

Research methods: In the experimental part of our study, to simulate diabetes, rabbits were intravenously injected with a 5% aqueous solution of alloxan (MolWeight: 244.13), at a dose of 100 mg/kg. In all experimental rabbits in which diabetes was modeled by administration of alloxan, regular dynamic monitoring of the development of diabetes was carried out; fasting blood glucose levels were determined using a glucometer (Senso Lite Nova, Budapest-Hungary) on days 5, 15, 30, 60 and 90 after administration 5 % aqueous solution of alloxan monohydrate. To obtain lymph from the thoracic lymphatic duct of a rabbit, the animal was fixed on its back to the operating table by its paws and upper jaw with a cushion placed under the shoulder blades. The operation was performed under anesthesia. Starting from the manubrium of the sternum, upward, a skin incision 4-6 cm long was made along the midline or 0.5-1.0 cm to the left. After creating the DM model, blood and lymph were collected from all animals to determine the parameters of the blood and lymph CAF system. studies of lipid metabolism indicators, lipid metabolism indicators, liver enzymes, pro- and anti-inflammatory cytokines, such as interleukin 4 (IL4), interleukin 6 (IL 6), tumor necrosis factor (TNF-alpha), as well as indicators of endothelial dysfunction endothelin-1(EN-1), vascular endothelial growth factor (VEGF), NO, C-reactive protein (CRP).

At the next stage of experimental research, various vascular complications were modeled. At this stage, 25 animals were separated to create models of myocardial infarction, unilateral femoral artery occlusion and unilateral renal artery occlusion, respectively. After creating various models of vascular complications, all of the above indicators in the circulatory and lymphatic systems were studied in these groups of animals.

In addition, only in the group with animals in which unilateral occlusion of the renal artery was modeled against the background of experimental diabetes (n = 25) was the mechanism of action of the drug glycyram studied.

In the clinical part of our study, all patients underwent general clinical and laboratory and instrumental studies. They underwent a

general as well as a biochemical blood test, including studies of the levels of creatinine, urea, uric acid, cystatin C, and lipid spectrum. In addition, indicators reflecting ED were determined - the concentration of En-1, NO, CRP, VEGF. Endothelium-dependent vasodilation (EDV) and endothelium-independent vasodilation (EIDV) of the brachial artery (BA) were studied using ultrasound. To assess the EDV of BA, a test inducing reactive hyperemia was performed. EIDV was determined by nitroglycerin test.

During the statistical analysis of the results obtained, the arithmetic mean (M), their standard error (m) and the average range of variation (min-max) were determined to characterize groups of homogeneous units. A nonparametric method for assessing the difference between indicators was used - the Mann-Whitney U test. Potential factors such as age and gender were introduced into the comparative analysis of the two groups. Differences between parameters in the study groups were considered significant at $p < 0.05$.

A quantitative characteristic of the dependence of the studied characteristics was presented on the basis of calculating indicators of the strength of the connection between them (correlation coefficients) and determining the dependence of one characteristic on changes in another (regression coefficient). To analyze the correlation between variables (indicators), Spearman's rank correlation coefficient (r) was used. Interpretation of correlation values: 0.2 - very weak, 0.2-0.5 - weak, 0.5-0.7 - average, 0.7-0.9 - strong, 0.9 - very strong. Differences between the compared variation series were regarded as statistically significant at the $p<0.05$ level. Statistical processing of the results obtained was carried out on a personal computer - in the electronic spreadsheet editor Microsoft Excel, and the results were processed using the IBM SPSS Statistics program.

The main provisions submitted for defense:

- In experimental diabetes, there is a pathogenetic relationship between endothelial dysfunction and disturbances in the processes of lipid peroxidation, cytokine status, functional activity of the liver, the CAF system and the composition of lipids in both the circulatory and lymphatic parts of humoral transport. As diabetes

progressed, these changes were most clearly revealed, reaching their maximum values. Also, these changes in the lymphatic link are unidirectional with shifts in the circulatory link, with some difference in the severity of changes in individual indicators.

- When modeling myocardial infarction against the background of experimental diabetes, as the period of development of this vascular complication increases, there is a worsening of disturbances in indicators of ED, LPO, cytokine profile, activity of liver enzymes, the CAF system and lipid composition in both the blood and lymph. In parallel, there is a worsening of lymphatic drainage both at the organismal and organ levels, which can be judged by the speed of lymph flow both from the thoracic duct and from the heart.
- Modeling of both occlusion of the artery of the lower limb against the background of experimental diabetes and occlusion of the renal artery is also accompanied by aggravation of endothelial dysfunction. These disorders are in direct relationship with disturbances in the processes of lipid peroxidation, cytokine status, functional activity of the liver, the CAF system and the composition of lipids in both the circulatory and lymphatic systems.
- Impaired lymphatic drainage of tissues, observed when modeling various vascular complications of diabetes (myocardial infarction, femoral artery occlusion and renal artery occlusion) is an important factor that will aggravate endothelial dysfunction, particularly in the circulatory system.
- The use of glycyram, which has a lymphotropic effect in case of occlusion of the renal artery against the background of experimental diabetes, prevents sharp disturbances in indicators of endothelial dysfunction, LPO, cytokine status, functional activity of the liver, the CAF system and the composition of lipids in the circulatory and lymphatic links.
- In patients with DN, the degree of impairment of endothelial function in the blood depends on the stage of DN. The most significant changes are observed at stages 3-4, as evidenced by a significant increase in the concentration of En-1, VEGF with a parallel decrease in NO.

- The use of glycyram in the complex treatment of DN improves EDV and depends on the stage of the disease. The effectiveness of this therapy is also manifested in a positive effect on the functional state of the kidneys in patients with DN in stages 1–3.

The scientific novelty of the research:

As a result of the studies, changes in ED were established for the first time in connection with disturbances in the processes of lipid peroxidation, cytokine profile, CAF system and lipid composition in the blood and lymph in experimental diabetes and its vascular complications such as myocardial infarction, occlusion of the renal artery and occlusion of the femoral artery of the lower extremity . A comparative analysis of the data obtained showed that in case of vascular complications against the background of experimental diabetes, ED disorders are observed not only at the circulatory level, but also at the lymphatic level. The deterioration of lymphatic drainage of tissues and organs is an additional factor that aggravates ED disorders in the bloodstream, which, in turn, subsequently leads to the development of serious complications.

For the first time, an adequate method has been developed for the correction of ED disorders due to occlusion of the renal artery against the background of experimental diabetes under the influence of glycyram. Improvement in lymphatic drainage of tissues and prevention of severe ED disorders have been shown when using glycyram for unilateral occlusion of the renal artery against the background of experimental diabetes.

An increase in the effectiveness of treatment of patients with diabetic nephropathy when glycyram is included in the complex of generally accepted basic therapy has also been shown.

The scientific and practical significance of the research:

In patients with diabetic nephropathy of various stages against the background of diabetes, there are significant changes in ED that correlate with the severity of diabetic nephropathy. In the clinic of this pathology, it should be taken into account that vascular disorders develop not only in the circulatory, but also in the lymphatic links. The inclusion of drugs with lymphatic action in the complex of therapy for

patients with diabetic nephropathy increases the effectiveness of their treatment.

The inclusion of glycyram, which has a lymphatic effect, in the complex of well-known sugar-lowering therapy for patients with diabetic nephropathy prevents severe ED disorders and increases the effectiveness of their treatment.

Approbation:

the main results of the dissertation were presented at the 6th International Conference of Health and Medical Sciences (Turkey, 2023), the 1st International Congress of Applied Sciences (Paris, 2023), and the scientific and practical conference "Current Problems of Medicine" (Baku, 2018) dedicated to the 100th anniversary of the Azerbaijan Republic.

A preliminary discussion of the dissertation work took place on June 23, 2023 at a joint meeting of employees of the Department of Internal Diseases I, II, III, Pathological Physiology, Clinical Pharmacology of the Azerbaijan Medical University (protocol №10). The dissertation work was discussed at the meeting of the Scientific Seminar of the Dissertation Council BED 2.27/1, operating on the basis of Azerbaijan Medical University (on February 28, 2024 (protocol №1).

Application of research results. The results of the research work were applied in the research work of the Department of Pathological Physiology and I Internal Medicine of Azerbaijan Medical University, as well as in the practical work of the Nephrology Department of the Educational and Therapeutic Clinic.

Name of the organization where thr dissertation is perfomed: Department of Internal Medicine I, Department of Pathological Physiology and Educational and Therapeutic Clinic of Azerbaijan Medical University.

Publications: the main provisions of the dissertation are reflected in 29 scientific works (17 articles and 12 theses).

Scope and structure of the dissertation: The dissertation is presented on 300 pages printed on a computer (323538 characters: title

page - 568, table of contents - 3983, introduction - 22174, Chapter I - 87282, Chapter II - 34033, Chapter III - 37501, Chapter IV - 62544. Chapter V – 15960, Chapter VI – 15594, Chapter VII – 9055, conclusions – 2711, Scientific significance of the work – 1109, Practical significance of the work 583, conclusion – 28169, list of abbreviations – 2272). The dissertation work is illustrated with 35 tables and 40 figures. The bibliography consists of 304 sources, covering authors from 7 local and 297 foreign countries.

MATERIALS AND METHODS OF RESEARCH

The study consisted of clinical and experimental parts. The experiments were carried out on 136 chinchilla breed rabbits of both sexes, weighing 2.5–3.0 kg. All surgical interventions necessary for the experiment were carried out under general anesthesia. Solutions of ketamine (8 mg/kg) and diphenhydramine (0.15 ml/kg 1% solution), which were administered intravenously, were used as anesthetic agents. In our studies, to simulate diabetes, rabbits were intravenously injected with a 5% aqueous solution of alloxan (Mol Weight: 244.13), at a dose of 100 mg/kg. In all experimental rabbits in which diabetes was modeled by administration of alloxan, regular dynamic monitoring of the development of diabetes was carried out; fasting blood glucose levels were determined using a glucometer (Senso Lite Nova, Budapest-Hungary) on days 5, 15, 30, 60 and 90 after administration 5 % aqueous solution of alloxan monohydrate. To obtain lymph from the thoracic lymphatic duct of a rabbit, the animal was fixed on its back to the operating table by its paws and upper jaw with a cushion placed under the shoulder blades. The operation was performed under anesthesia. Starting from the manubrium of the sternum, upward, a skin incision 4-6 cm long was made along the midline or 0.5-1.0 cm to the left. After creating the DM model, blood and lymph were collected from all animals to determine the parameters of the blood and lymph CAF system. studies of lipid metabolism indicators, lipid metabolism indicators, liver enzymes, pro- and anti-inflammatory cytokines, such as interleukin 4 (IL 4), interleukin 6 (IL

6), tumor necrosis factor (TNF-alpha), as well as indicators of endothelial dysfunction endothelin-1 (EN-1), vascular endothelial growth factor (VEGF), nitric oxide (NO), C-reactive protein (CRP).

At the next stage of experimental research, various vascular complications were modeled. At this stage, 25 animals were separated to create models of myocardial infarction, unilateral femoral artery occlusion and unilateral renal artery occlusion, respectively. After creating various models of vascular complications, all of the above indicators in the circulatory and lymphatic systems were studied in these groups of animals.

In addition, only in the group of animals in which unilateral renal artery occlusion was modeled against the background of experimental diabetes (n = 25), the effect of the drug glycyram was studied. In the clinical part of the study, 120 patients with DN aged from 25 to 60 years were examined. Of these, 60 patients were female (50%), 60 were male (50%). The study included patients with stages 1-4 DN. The stages of DN were determined according to the DN classification (NCBI 2014). All patients included in the study underwent general clinical and laboratory and instrumental studies. They underwent a general as well as a biochemical blood test, including studies of the levels of creatinine, urea, uric acid, cystatin C, lipid spectrum, IL 6, IL 10, TNF-alpha. In addition, indicators reflecting ED were determined - the concentration of En-1, NO, CRP, VEGF. Endothelium-dependent vasodilation (EDV) and endothelium-independent vasodilation (EIDV) of the brachial artery (BA) were studied using ultrasound. To assess the EDV of BA, a test inducing reactive hyperemia was performed. EIDV was determined by nitroglycerin test.

During the statistical analysis of the results obtained, the arithmetic mean (M), their standard error (m) and the average range of variation (min-max) were determined to characterize groups of homogeneous units. A nonparametric method for assessing the difference between indicators was used - the Mann-Whitney U test. Potential factors such as age and gender were introduced into the comparative analysis of the two groups. Differences between parameters in the study groups were considered significant at $p < 0.05$.

A quantitative characteristic of the dependence of the studied characteristics was presented on the basis of calculating indicators of the strength of the connection between them (correlation coefficients) and determining the dependence of one characteristic on changes in another (regression coefficient). To analyze the correlation between variables (indicators), Spearman's rank correlation coefficient (r) was used. Interpretation of correlation values: 0.2 - very weak, 0.2-0.5 - weak, 0.5-0.7 - average, 0.7-0.9 - strong, 0.9 - very strong. Differences between the compared variation series were regarded as statistically significant at the $p<0.05$ level. Statistical processing of the results obtained was carried out on a personal computer - in the electronic spreadsheet editor Microsoft Excel, and the results were processed using the IBM SPSS Statistics program.

RESEARCH RESULTS AND DISCUSSION

Experimental results

In 25 animals, after modeling alloxan diabetes, blood and lymph were studied, as well as the speed of lymph flow. When modeling diabetes, such indicators of ED in the blood as En-1, NO and EF were subject to very significant changes. Thus, after 5 days of the study, the most noticeable changes were recorded in relation to En-1, which after modeling DM increased, exceeding the normative values by 62.5% ($p <0.001$). This dynamics of changes in endothelin-1 content persisted until the end of the study. All this led to the fact that the content of En-1 in the blood by the end of the study exceeded the initial level by more than 3.2 times ($p <0.001$). The same dynamics of changes were observed when studying another indicator of ED - EF. The EF study showed that after 5 days of the study, the level of EF in the blood increased slightly (by 18.0%). However, maintaining such dynamics throughout the experiment contributed to an increase in the level of VWF in the blood to 158.4% of the initial value ($p <0.001$). It should be noted that against this background, the NO content in the blood, on the contrary, gradually decreased, and by the end of the study - to 63.8% ($p <0.001$).

The study of indicators of cytokine status in the blood after modeling diabetes mellitus also revealed pronounced changes. There was a significant increase in the levels of both pro-inflammatory and anti-inflammatory cytokines. So, 5 days after modeling, the levels of TNF-α, IL-4 and IL-6 in the blood increased by 20.5%, 25.5% and 13.6%, respectively, ($p<0.05$-0.001) and this the trend continued in subsequent periods of the study. On the 30th day, after modeling, the levels of TNF-α, IL-4 and IL-6 exceeded the initial values by 3.2 times ($p<0.001$), 2.4 times ($p<0.001$) and 2.5 times ($p<0.001$), respectively. During the subsequent periods of the study, the content of TNF-α and IL-6 continued to increase, and on days 60 and 90 it was more than 4.5 times and 3.5 times higher than the initial levels, respectively ($p < 0.001$). Changes in the content of IL-4 in the dynamics of observation were somewhat different: starting from the 30th day of the study, the level of IL-4, in contrast to TNF-α and IL-6, began to decrease on the contrary, and after 60 days it was less than in the initial state by almost 97.8 %($p<0.001$), however, on day 90 it increased by 36.2%($p<0.001$) in comparison with the level from the corresponding initial indicator.

When modeling diabetes, ED indicators in the lymph also underwent significant changes. Within 5 days after the administration of a 5% aqueous solution of alloxan, the content of endothelin increased by 35.4% ($p<0.01$) compared to the initial indicator. The same dynamics were observed in the level of EF. LPO indicators underwent the most significant changes after 5 days of the study. Noticeable changes in cytokines were recorded starting from the 5th day of the study: the levels of TNF-α and IL 4 compared to the corresponding indicators in the initial state increased by 23.5% and 25.5%, and by the end of the study, this was more than 5.5 times, 3.2 times, respectively ($p<0.001$).

Thus, the results of the study showed that modeling of diabetes led to significant changes in ED indicators, as well as LPO, cytokine status and liver enzyme activity in the blood.

When comparing indicators of ED, LPO, cytokine status and liver enzyme activity in the blood and lymph, it turned out that modeling diabetes in rabbits leads to unidirectional changes in the studied

indicators in the blood and lymph. This is also clearly evidenced by the graphical representation of the shifts in the studied parameters in the blood and lymph, presented in Figure 1.

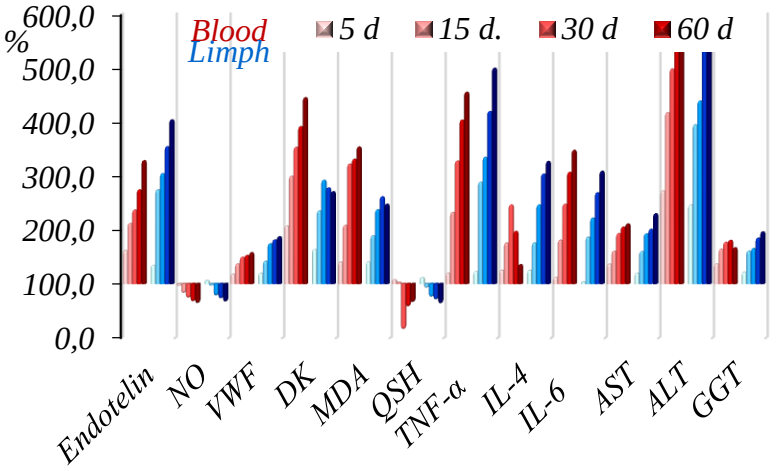


Figure 1. Comparative dynamics of ED and LPO indicators, cytokine status and liver enzyme activity in the blood and lymph when modeling experimental diabetes

Throughout the study period, the dynamics of endothelial dysfunction indicators in the blood and lymph were the same. Starting from the 5th day of the study, the level of En-1 significantly exceeded the initial level in the blood (by 62.5%) and in the lymph (by 35.0%), maintaining such dynamics until the end of the study ($p < 0.01$-0.001) . The same dynamics were observed when studying the content of VWF in both blood and lymph. 5 days after the administration of a 5% aqueous solution of alloxan, the content of PV in both liquid media, compared with the corresponding initial indicators, noticeably increased by 20.1% and 18.4% ($p < 0.05$), respectively. By the end of the study, these indicators exceeded the corresponding initial values by 58.4% and 88.0% ($p<0.001$), respectively, in the blood and lymph. However, the dynamics of NO differed from the dynamics of En-1 and

VWF. After modeling diabetes, the NO level did not undergo significant changes during the 30th day of the study, and then began to decrease, and within 90 days reached 63.8% (in the blood) and up to 66.6% (in the lymph) of the corresponding initial value ($p<0.001$).

Indicators of cytokine status both in the blood and lymph also underwent significant changes. When comparing the data obtained, it turned out that modeling DM in rabbits led to unidirectional changes. Thus, in both liquid media the concentration of not only pro-inflammatory, but also anti-inflammatory cytokines increased, starting from the 5th day of the study. Modeling of diabetes in rabbits was also accompanied by unidirectional, very significant changes in the activity of liver enzymes in the blood and lymph. Noticeable changes were recorded after 5 days of the study. Subsequently, as the observation period increased, the activity of the studied liver enzymes steadily increased both in the blood and in the lymph.

At this stage of research, a comparative study of coagulation parameters and lipid composition in the blood and lymph was also carried out when modeling alloxan diabetes. When comparing the studied individual indicators of blood and lymph coagulation, as well as indicators of lipid composition in the blood and lymph, mainly unidirectional changes were also observed, the differences concerned mainly the degree of severity of the changes. Figure 2 shows the comparative dynamics of coagulation parameters and lipid composition of blood and lymph when modeling diabetes.

The direction of shifts in aPTT in blood and lymph did not differ; in both environments this indicator underwent noticeable changes after 15 days of the study and within 60 days shortened to the maximum, amounting to 76.1% in blood and 81.6% of the corresponding initial value in lymph ($p <0.05$).

In both liquid media, the concentration of atherogenic lipids steadily increased during the entire observation against the background of a decrease in the concentration of HDL ($p <0.001$).

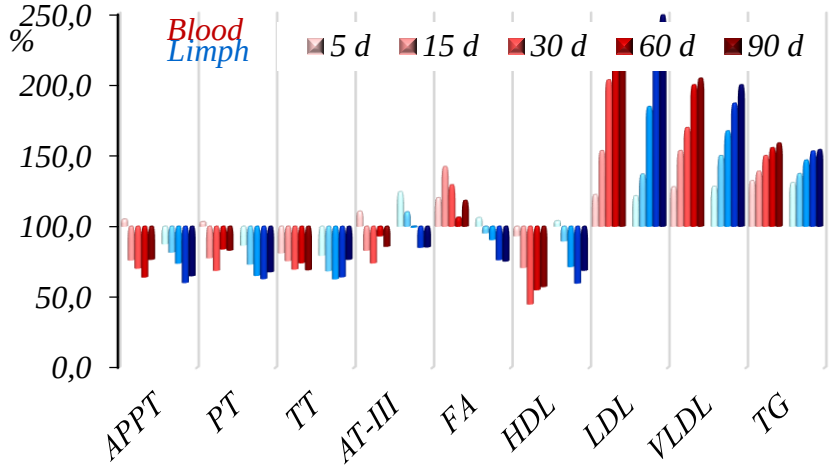


Figure 2. Comparative dynamics of coagulation parameters and lipid composition in the blood and lymph when modeling alloxan diabetes

The results of the study of the drainage function of the lymphatic system at the organismal and organ levels are presented in Figure 3.

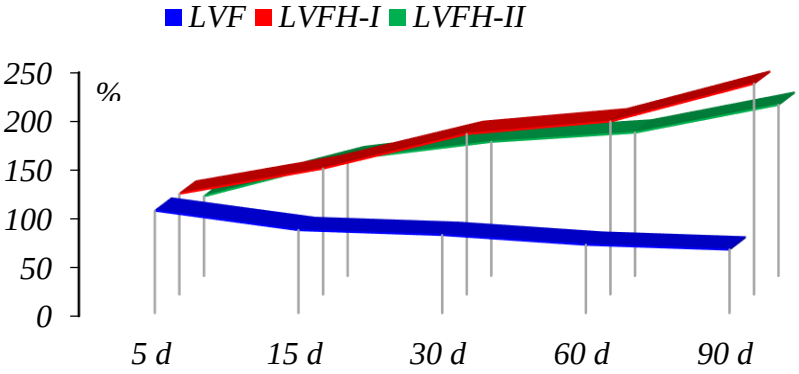


Figure 3. Indicators of the drainage function of the lymphatic system at the organismal and organ levels when modeling diabetes (M±m; n=21)

Summarizing the above discussion of our own research data in this series of experiments, we can conclude that modeling diabetes in rabbits leads mainly to unidirectional changes in the studied parameters, both in the blood and in the lymph. All this indicates that when modeling diabetes, favorable conditions are created for the occurrence of vascular disorders not only in the circulatory but also in the lymphatic systems. A comparison of the data from this study with literature data leads us to believe that in diabetic angiopathy, not only the supply of oxygen and nutrients to tissues and organs is disrupted, but also the removal of toxic metabolites, the remains of destroyed cells and large molecular particles from the intercellular space and from the vascular microenvironment. All this ultimately aggravates vascular disorders and destructive processes in tissues and organs with all the ensuing consequences. And vascular disorders, as noted above, are the main cause of mortality in diabetes, in the pathogenesis of which ED has recently been assigned an important role.

At the next stage of research, myocardial infarction was simulated in 25 animals against the background of experimental diabetes. In this group of animals, in addition to the studied parameters of blood and lymph, as well as lymphatic drainage of tissues, the state of lymphatic drainage of the heart was also studied during the same time periods as in previous series of studies.

Figure 4 shows the comparative dynamics of changes identified when modeling myocardial infarction against the background of experimental diabetes in the blood and lymph. As can be seen from this figure, the detected shifts in the blood and lymph are also unidirectional. Thus, the levels of En-1 and VWF exceeded the corresponding initial indicators, already after 5 days of the study and as the study period increased, they maintained such dynamics of change. At the same time, the dynamics of changes in NO were different, a noticeable decrease in the level of NO in the blood was observed after 15 days of the study, and the level of NO in the lymph - after 30 days of the study ($p < 0.001$) and these dynamics \persisted until the end of the study.

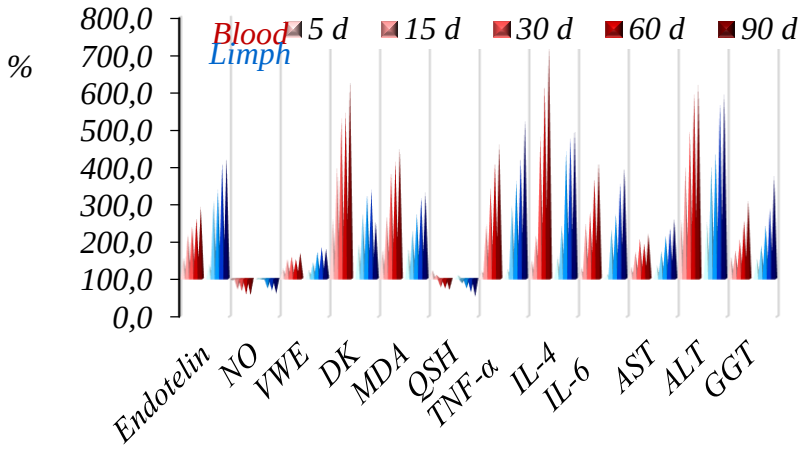


Figure 4. Comparative dynamics of changes in indicators of ED, LPO, cytokine status and liver enzyme activity in the blood and lymph when modeling myocardial infarction against the background of experimental diabetes

The cytokine composition of blood and lymph also underwent very pronounced changes. At the same time, in both liquid media, the levels of not only pro- but also anti-inflammatory cytokines, such as TNF-α, IL 4 and IL 6, increased. The identified changes in the content of pro- and anti-inflammatory cytokines in the blood and lymph gradually worsened as the study period increased and, by the end of the study, reached their maximum values, exceeding the corresponding initial values in the blood by more than 4.5 times, 7.2 times and 4.1 times, and in the lymph by more than 5.2 times, 5. 0 times and 3.9 times, respectively ($p<0.001$).

Figure 5 illustrates comparative images of the dynamics of changes in the studied parameters of coagulation and lipid metabolism in the blood and lymph when simulating myocardial infarction against the background of experimental diabetes. As can be seen from the presented figure, the identified shifts in the blood and lymph of the studied indicators of coagulation and lipid metabolism in this group of animals were mainly of a unidirectional nature; the existing

differences in the identified shifts concerned mainly the degree of shifts. The maximum reduction in aPTT both in the blood and in the lymph was recorded after 30 days of the study, however, in the blood up to 56.5%, and in the lymph up to 70.3% of the corresponding norm ($p < 0.01$-0.001). Subsequently, a reverse wave of shifts was observed in both fluids - in the blood this indicator increased to 64.9%, and in the lymph - to 76.3% of the corresponding initial indicator ($p < 0.01$). When comparing other indicators of coagulation in blood and lymph, the same picture was observed.

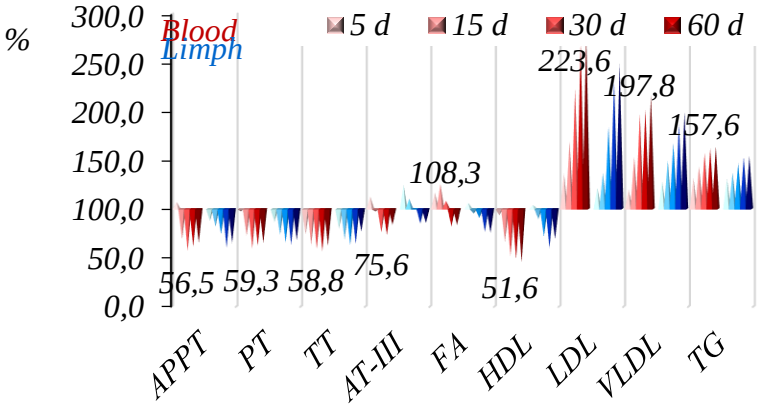


Figure 5. Comparative dynamics of changes in coagulation parameters and lipid metabolism in the blood and lymph when simulating myocardial infarction against the background of experimental diabetes

Lipid metabolism indicators also underwent similar changes. Thus, as the study period increased, in both liquid media (blood and lymph) the content of atherogenic lipids, such as low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and triglycerides (TG), increased against the background of a decrease in the content of high-density lipoproteins (HDL). However, these changes were most pronounced in the blood than in the lymph. For example, by the end of the study, the level of LDL in the blood exceeded the initial level by more than 2.8 times, and in the lymph by more than 2.4 times (p

<0.001), the level of VLDL exceeded the norm by more than 2. 1 time, and in the lymph more than 2.0 times (p <0.001). The HDL content gradually decreased over the course of observation and until the end of the study it was lower in the blood to 45.0%, and in the lymph to 57.3% of the corresponding initial value (p <0.001).

Thus, the results of a comparative analysis of the data obtained showed that when modeling myocardial infarction against the background of experimental diabetes, the indicators of coagulation and lipid metabolism in the blood and lymph were subject to unidirectional changes.

The results of the study of the drainage function of the lymphatic system at the organismal and organ levels (heart) are presented in Figure 6. The figure shows that modeling myocardial infarction against the background of diabetes had a negative effect on the drainage function of the lymphatic system, both at the organismal and regional levels.

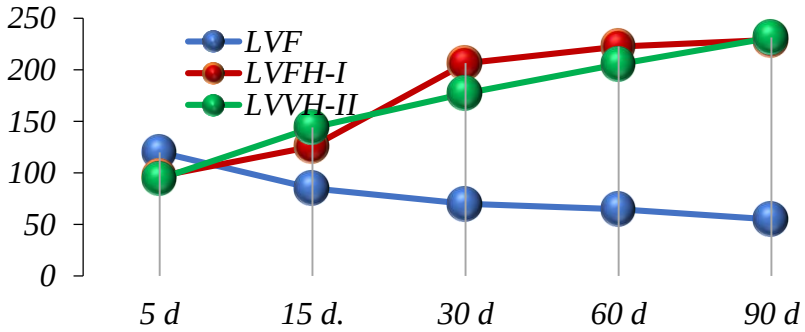


Figure 6. Changes in indicators of the drainage function of the lymphatic system at the organismal and organ levels when modeling myocardial infarction against the background of experimental diabetes

Inhibition of the drainage function of the lymphatic system in the heart was observed until the end of the study. At this stage of the study,

the time of removal of the lymphotropic dye at the first stage significantly exceeded the initial level.

When modeling unilateral femoral occlusion arteries against the background of experimental diabetes, very pronounced shifts in the studied indicators of ED (En-1, NO, VWF) in the blood and lymph were also revealed. Figure 7 shows the comparative dynamics of changes identified when modeling unilateral occlusion of the femoral artery against the background of experimental diabetes in the blood and lymph. As can be seen from this figure, the shifts in ED, LPO, cytokine status and liver enzyme activity observed in the blood and lymph are unidirectional.

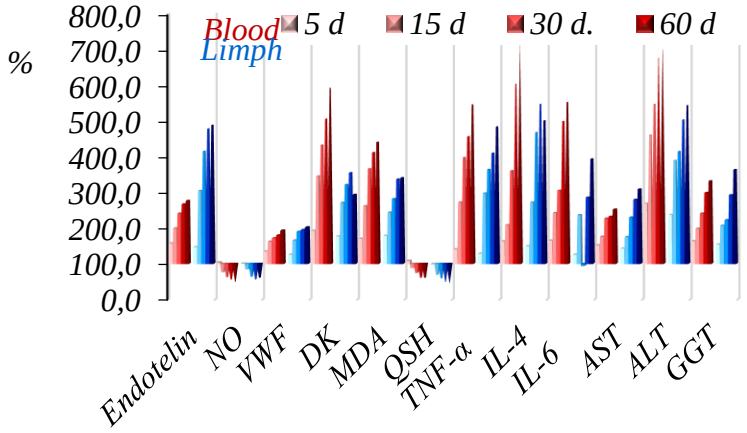


Figure 7. Comparative dynamics of changes in indicators of ED, LPO, cytokine status and liver enzyme activity in the blood and lymph when modeling unilateral occlusion of the femoral artery against the background of experimental diabetes

Thus, the levels of endothelin-1 and VWF both in the blood and lymph increased after 5 days of the study, exceeding the corresponding initial and control indicators, with maximum shifts by the 90th day of the study. The maximum decrease in the level of NO both in the blood and in the lymph was recorded by the 90th day of the study (less than

the initial level in the blood by 52.4%, in the lymph by 38.2% $p < 0.001$).

A comparative analysis of changes in the content of pro- and anti-inflammatory cytokines both in the blood and lymph showed that the level of the latter increased as the study period increased.

Thus, the results of a comparative analysis of the data obtained showed that modeling of unilateral femoral artery occlusion against the background of experimental diabetes promotes unidirectional changes in ED indicators, cytokine status and liver enzyme activity in both the blood and lymph, with some differences in the severity of individual indicators. Figure 8 shows the comparative dynamics of changes in the studied parameters of coagulation and lipid metabolism in the blood and lymph after modeling unilateral occlusion of the femoral artery against the background of experimental diabetes. The unidirectionality of the identified changes was evidenced by the determination of the values of aPTT, TT, PT, AT and markers of intravascular coagulation both in the blood and lymph throughout the observation. Significant changes were mainly observed starting from the 15th day of the study, with aggravation of the disorders by the 60-90th day of the experiment.

Similar changes were noted in lipid metabolism parameters. As the study period increased, the content of atherogenic lipids - LDL, VLDL and TG - increased in both the blood and lymph against the background of a decrease in the HDL content. These changes in the comparative aspect in terms of the level of most indicators were more pronounced in the lymph than in the blood.

In the next group of animals (n=25), unilateral occlusion of the renal artery against the background of experimental diabetes was modeled. Studies of the studied parameters in the blood and lymph were carried out in the same time periods as in previous series of the study.

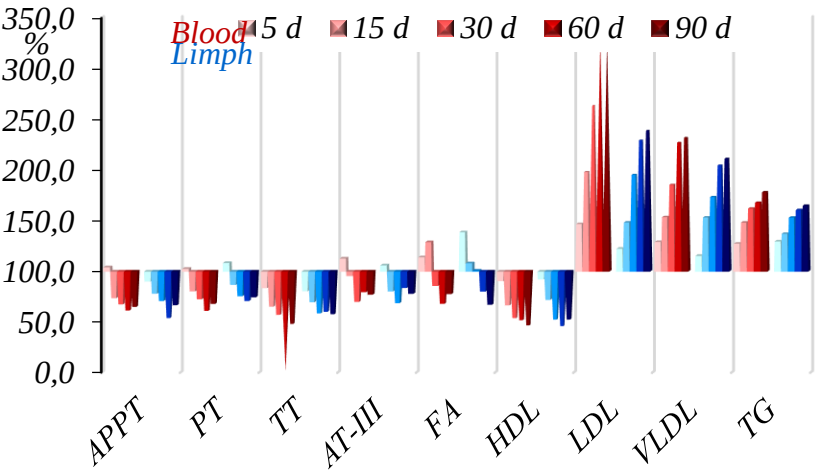


Figure 8. Comparative dynamics of changes in coagulation parameters and lipid metabolism in the blood and lymph, when modeling unilateral occlusion of the femoral artery against the background of experimental diabetes

Comparative dynamics of detected changes in the blood and lymph after modeling unilateral occlusion of the renal artery against the background of experimental diabetes in the blood and lymph are presented in Figure 9.

As can be seen from the figure, the shifts in the indicators of ED, LPO, cytokine status and liver enzyme activity in the blood and lymph were unidirectional in nature with certain differences in the degree of expression in relation to certain indicators at the corresponding periods of the study.

The levels of En-1 and VWF, both in the blood and in the lymph, exceeded the corresponding initial indicators, and more in the lymph compared to the blood at all times of the study. At the same time, a more pronounced decrease in NO was more detected in the blood than in the lymph during all periods of the study.

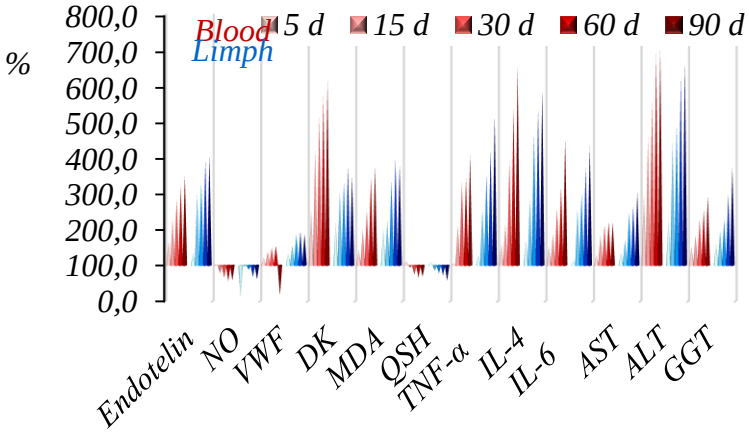


Figure 9. Comparative dynamics of changes in indicators of ED, LPO, cytokine status and liver enzyme activity in the blood and lymph when modeling unilateral renal occlusion

A comparative analysis of changes in lipid peroxidation processes and the level of antioxidant activity showed that the nature of changes in both liquid media was also unidirectional.

The cytokine composition of blood and lymph also underwent similar changes. The identified changes in the cytokine composition in the blood and lymph, also having differences in the severity of the level of TNF-alpha, IL-4 and IL-6, also had unidirectional changes in both humoral environments of the body. At the same time, the gradual increase in the content of cytokines as the study period increased reached its maximum values by the end of the study, moreover, more in the blood compared to lymph. Comparison of changes in the activity of the studied liver enzymes both in the blood and in the lymph revealed a similar nature of changes.

Thus, the results of a comparative analysis of the data obtained showed that modeling of unilateral renal artery occlusion against the background of experimental diabetes promotes unidirectional changes

in indicators of ED, LPO, and cytokine status in both the blood and lymph with a certain difference in the level of individual indicators.

A comparative description of changes in the studied parameters of the hemostasis system and lipid metabolism in the blood and lymph in this group of experimental studies was also carried out. A comparative analysis showed that the nature of changes in blood coagulability and lymph was unidirectional, while hypercoagulable changes were observed, more pronounced in the blood compared to lymph.

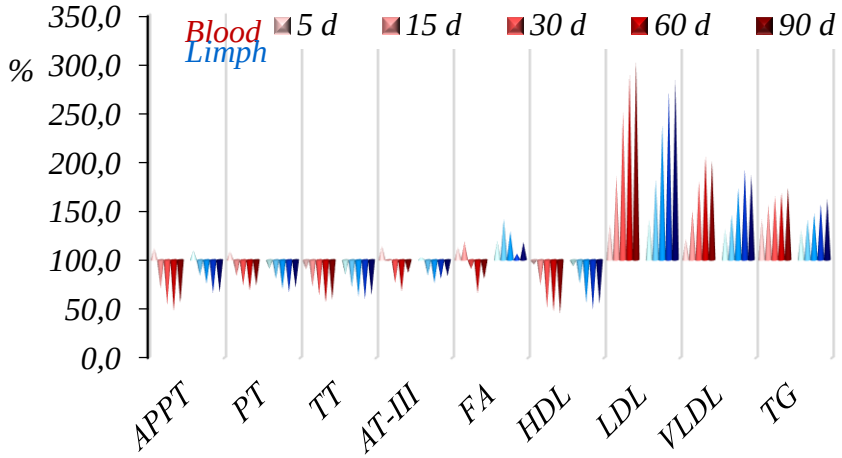


Figure 10. Comparative dynamics of changes in coagulation and lipid metabolism in the blood and lymph when modeling unilateral renal artery occlusion against the background of experimental diabetes

As can be seen from Fig. 10, significant shifts towards increased coagulability compared to the corresponding initial values were noted starting from the 30th day of the study both in the blood and in the lymph and persisted until the end of the experiment (decrease in aPTT, PT, TT). One direction of hypercoagulable changes with an increased risk of thrombosis in the blood and lymph was evidenced by the

identification of markers of intravascular coagulation during all periods of observation.

A similar pattern of changes in lipid metabolism was also observed both in the blood and in the lymph. The most pronounced increase in the level of atherogenic lipids, such as LDL, VLDL and TG, against the background of a decrease in HDL content as the study period increased, was observed in both liquid media.

Thus, the results of a comparative analysis of the data obtained showed that when modeling unilateral occlusion of the renal artery against the background of experimental diabetes, the indicators of coagulation and lipid metabolism in the blood and lymph were subject to unidirectional changes.

Summarizing the results of studies on the study of ED indicators in the pathogenetic relationship with disturbances in the processes of lipid peroxidation, cytokine status, functional activity of the liver, lipid composition and the CAF system in the circulatory and lymphatic links when modeling vascular complications against the background of experimental diabetes, we can say that for all vascular complications - When modeling myocardial infarction, unilateral occlusion of the femoral artery and unilateral occlusion of the renal artery against the background of diabetes, unidirectional disorders are revealed in both the blood and lymph with parallel inhibition of lymphatic drainage of tissues.

The most pronounced changes in severity are observed when modeling myocardial infarction, then when modeling unilateral renal artery occlusion and, finally, when modeling unilateral femoral artery occlusion against the background of experimental diabetes.

At the next stage of experimental studies, 25 rabbits, after modeling renal artery occlusion against the background of experimental diabetes, were treated with glycyram. Blood and lymph for biochemical analyses, as well as the state of the drainage function of the lymphatic system,

were determined at the same time periods as in previous series of studies.

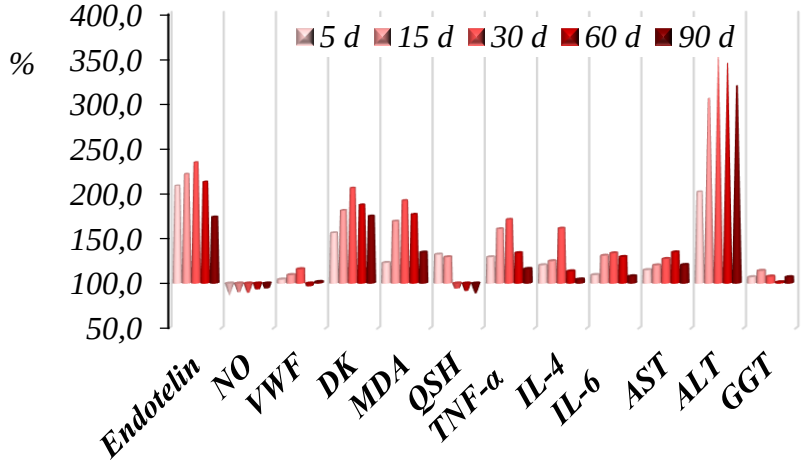


Figure 11. Dynamics of changes in indicators of ED, LPO, cytokine status and liver enzyme activity in the blood in animals after modeling renal artery occlusion against the background of experimental diabetes under conditions of glycyram use

Figure 10 shows data on the study of indicators of ED, LPO, cytokine status and liver enzyme activity in the blood under conditions of glyceram use. In this group of animals, the levels of En-1 and NO decreased significantly not only compared to the corresponding initial values, but also compared to the data from the corresponding control group without the use of glycyram. The peak of En-1 shifts in the blood compared to the initial values was observed after 30 days of the study (2.4 times more compared to the initial value), and compared to the corresponding control values it was half as much by the end of the study ($p < 0.05$). At the same time, the NO content in the blood on the 15th day of the study was less than the initial values by only 15%. In comparison with the group without the use of glycyram, the level of NO in the blood, starting from the 15th day, was already higher and these

dynamics of changes persisted throughout the experiment. The level of VWF was also lower, compared to the group without treatment, already from the 5th day and on the 60th day its content in the blood was 36% less.

A comparatively pronounced prevention of sudden changes was also noted in lipid peroxidation processes after the use of glycyram. At the same time, the levels of diene conjugates and malondialdehyde in the blood maximally exceeded the initial levels on the 30th day (on average 2 times) but compared with the group without the use of glycyram at all periods of the study it was less 18%. The contents of all studied pro- and anti-inflammatory cytokines in the blood, compared with the corresponding initial indicators, were maximally increased on day 30. The maximum increase in the content of TNF-α, IL-4 and IL-6 in the blood compared to the initial data during this period was greater on average by 70%, 61% and 34%, respectively, and in comparison with the group without the use of glycyram it was less on average by 34%, 50% and 49%, respectively. Thus, the results of studies of indicators of ED, LPO, cytokine status and in the blood in animals after modeling renal artery occlusion against the background of experimental diabetes under conditions of glycyram use showed that the use of glycyram led to a pronounced correction of the disorders noted after modeling renal artery occlusion against the background of experimental diabetes.

Figure 11 shows changes in indicators of ED, LPO, cytokine status and liver enzyme activity in the lymph under the influence of glycyram after modeling renal artery occlusion against the background of experimental diabetes. The levels of En-1, NO and VWF, as well as in the blood, decreased significantly in comparison with the initial data and, accordingly, after the use of glycyram. More pronounced changes were noted in the decrease in the level of NO and VWF starting as early as 5 days after glycyram administration, while the level of endothelin 1 decreased significantly starting from 60 days (by an average of 33%).

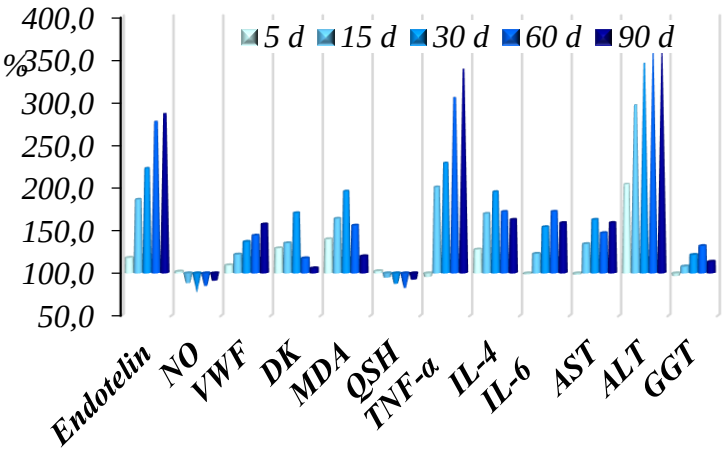


Figure 12. Dynamics of changes in indicators of ED, LPO, cytokine status and liver enzyme activity in the lymph in animals after modeling renal artery occlusion against the background of experimental diabetes under conditions of glycyram use (M±m; n=25)

Relatively pronounced positive changes were also noted in the cytokine profile of the lymph. The contents of all studied pro- and anti-inflammatory cytokines in the lymph increased significantly less compared to the corresponding initial indicators and were less than in the group without the use of glycyram. Thus, the results of our studies indicated the corrective effect of glycyram on pronounced disturbances in the levels of ED, LPO, cytokine status and liver enzyme activity in animals after modeling renal artery occlusion against the background of experimental diabetes, not only in the blood, but also in the lymph.

The comparative dynamics of the changes noted showed that after the use of glycyram under conditions of renal artery occlusion modeled against the background of experimental diabetes, both in the blood and in the lymph, a pronounced corrective effect of glycyram was noted;

there were only some digital differences in the degree of influence relative to individual indicators.

Figures 13 and 14 show, respectively, changes in coagulation parameters and lipid metabolism in the blood and lymph under the influence of glycyram after modeling renal artery occlusion against the background of experimental diabetes.

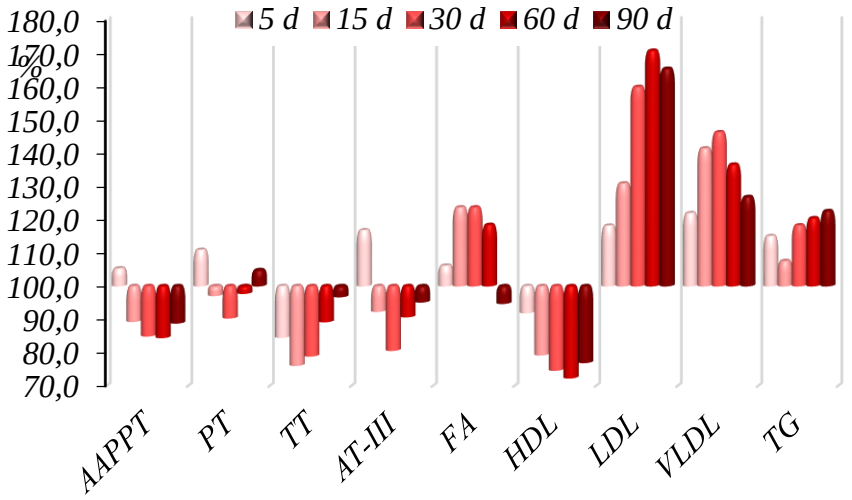


Figure 13. Changes in coagulation parameters and lipid metabolism in the blood under the influence of glycyram after modeling renal artery occlusion against the background of experimental diabetes

As can be seen from the figures, the use of glycyram after modeling renal artery occlusion against the background of experimental diabetes in experimental animals prevented sharp changes in blood and lymph coagulation. At the same time, the aPTT in the blood on the 15th day of the study was less than the initial data by an average of 76%, but compared with the data in the group without treatment it was longer on

average by 20%, while in the lymph the aPTT value during all periods of the study was less compared to with the data from intact animals by an average of 11% -19%, and compared with the data in the group without the use of glycyram it steadily increased (starting from 15 days - by an average of 30%, on the 30th day - by an average of 36% and on the 60th day - on average by 66%, and by the end of the experiment - by an average of 69%).

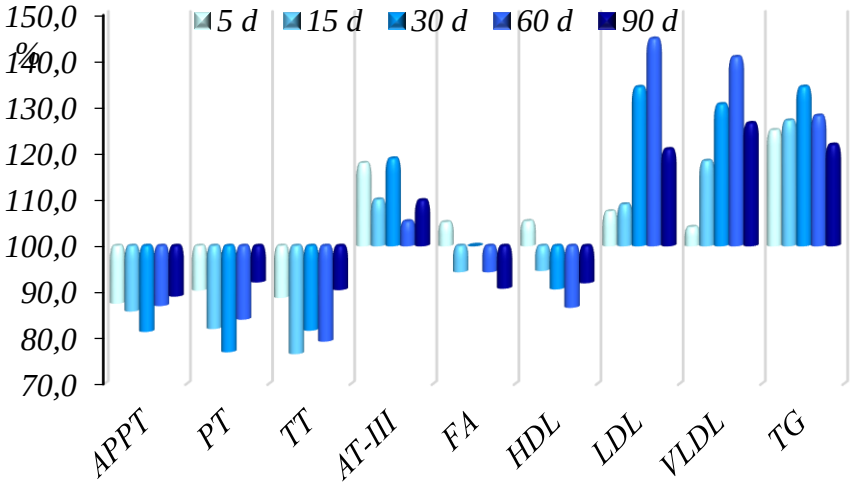


Figure 14. Dynamics of coagulation parameters and lipid composition in the lymph after modeling renal artery occlusion against the background of experimental diabetes under conditions of glycyram use (M±m; n=25)

Studies of lipid metabolism in the blood and lymph also showed that the use of glycyram after modeling renal artery occlusion against the background of experimental diabetes helped prevent pronounced changes in lipid composition. Thus, very noticeable changes in the content of LDL and VLDL in the blood in comparison with the values

of the corresponding indicators in the group without treatment were recorded starting from the 15th day of the study. In subsequent periods, this trend increased even more and on day 60 the content of LDL and VLDL was greater than the value of intact animals by an average of 71% and 37%, respectively, and less than in the group without treatment by 38% and 42%. The study of lipid metabolism in the lymph also showed that the use of glycyram after modeling renal artery occlusion against the background of experimental diabetes improved the picture of the lipid spectrum of the lymph as compared with data from a group of animals without the use of glycyram. The level of LDL and VLDL decreased significantly starting from the 30th day of the study, which was followed until the end of the study. 60 and 90 days after the use of glycyram, the maximum reduction was recorded compared to the data in the group without the use of glycyram (on average by 32% and 45% for LDL and by 24% and 29% for VLDL).

Parallel tracking of lymph flow velocity (LFV) from the drained thoracic duct after the use of glycyram showed a significant acceleration of LFV, and these changes exceeded the values of intact animals, starting from the 30th day of the study (Fig. 15).

Thus, the results of studies in this group showed that the use of glycyram after modeling renal artery occlusion against the background of experimental diabetes had a corrective effect and eliminated pronounced disorders of coagulation and lipid composition in both the blood and lymph. A pronounced stimulating effect on the LFV indicated the lymphotropic effect of glycyram and its positive effect on the dynamics of acute renal artery occlusion against the background of experimental diabetes.

The data obtained provided the basis for testing the use of glycyram in the complex treatment of patients with impaired renal function due to diabetes.

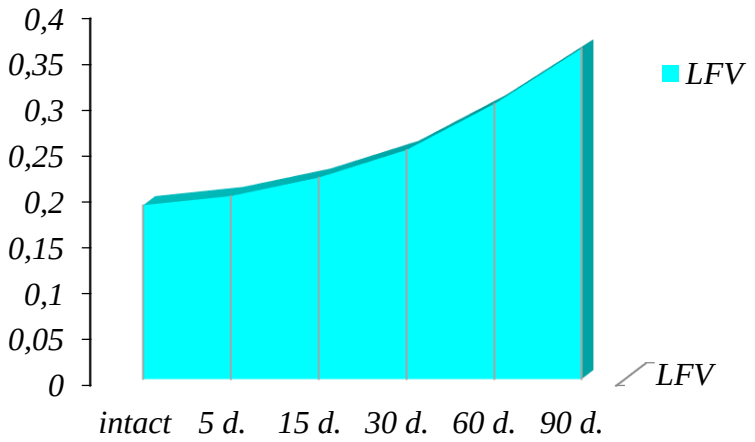


Figure 15. Dynamics of LFV after modeling renal artery occlusion against the background of experimental diabetes under conditions of glycyram use (M±m)

Clinical trial results

At this stage of the research, an analysis of parameters reflecting the function of the vascular endothelium depending on the stage and nosology of diabetic nephropathy was carried out, as well as an assessment of parameters reflecting the function of the endothelium in the blood in diabetic nephropathy and changes in the systemic response to inflammation.

During the study, in order to assess the functional state of the vascular endothelium, we determined the level of EN-1, NO, VEGF in the blood, the concentration of inflammatory markers, cytokines IL-4, Interleukin 6 (IL-6), TNF-alpha, and studied the systemic response to inflammation . The results obtained were compared between groups (Table 1).

Table 1

Functional biomarkers of endothelium in the blood in DN

Markers	DN (n=120)			
	I n=30	II n=30	III n=30	IV n=30
Endotelin-1 fmol/ml	1,13±0,085 (0,49-1,62)	2,16±0,292 (0,55-4,25) p_1<0,05	3,11±0,288 (1,2-5,10) p_1<0,001 p_2<0,05	4,25±0,412 (1,5-7,12) p_1<0,001 p_2<0,001 p_3<0,001
NO, мкmol/ml	24,8±2,37 (9,7-42,5) (20,7-22,4)	24,8±0,73 (20,7-39,5) p_1>0,05	18,6±0,84 (11,5-24,1) p_1<0,05 p_2<0,001	14,0±0,94 (8,3-21,8) p_1<0,001 p_2<0,001 p_3<0,05
VEGF pg/ml	158,1±5,63 (115,0-193,6) (167,0-193,6)	176,2±8,54 (126,3-227,0) p_1>0,0	241,8±2,97 (214,4-265,0) p_1<0,001 p_2<0,001	285,0±4,16 (219,0-309,0) p_1<0,001 p_2<0,001 p_3<0,001
IL-10 pg/ml	7,4±0,42 (3,5-13,2)	8,6±0,58 (4,2-15,9) p_1>0,05	21,2±1,57 (6,8-35,7) p_1<0,001 p_2<0,001	25,8±1,69 (11,2-42,5) p_1<0,001 p_2<0,001 p_3>0,05
IL-6 pg/ml	1,4±0,09 (,78-2,21)	2,1±0,20 (,76-5,40) p_1<0,05	5,5±0,49 (1,86-10,90) p_1<0,001 p_2<0,001	7,0±0,72 (1,88-17,90) p_1<0,001 p_2<0,001 p_3>0,05
TNFα pg/ml	3,9±0,23 (1,3-5,9)	3,1±0,31 (1,4-7,6) p_1<0,05	25,5±1,93 (7,6-42,1) p_1<0,001 p_2<0,001	32,0±1,58 (15,6-46,1) p_1<0,001 p_2<0,001 p_3<0,001
CRP, mg/ml	11,1±0,78 *# (4,2-17,9)	16,6±1,23*# (9,4-35,3) p_1<0,001	22,0±1,58 *# (11,8-45,2) p_1<0,001 p_2>0,05	27,9±2,44*# (11,7-63,2) p_1<0,001 p_2<0,01 p_3<0,05

When determining the concentration of EN-1 in the blood of group I, it was found that its level is high - 1.13±0.08 fmol/ml already from the 1st stage of DN. For stages 2 and 3, the concentration of EN-1 was very high - 2.16 ± 0.292 fmol/ml and 3.11 ± 0.288 fmol/ml, respectively. At the 4th stage, the average level of EN-1 was 4.25±0.412 fmol/ml, and in the 4th group there were no cases of its concentration less than 1.5 fmol/ml

The concentration of EN-1 was statistically significantly higher at stages 2 and 3 compared to the previous stage ($p<0.05$). In group 4, the maximum value was 7.12 fmol/ml and a statistically significant difference was revealed compared to other groups ($p <0.001$). The results of the comparative analysis carried out by group are shown in Figure 16.

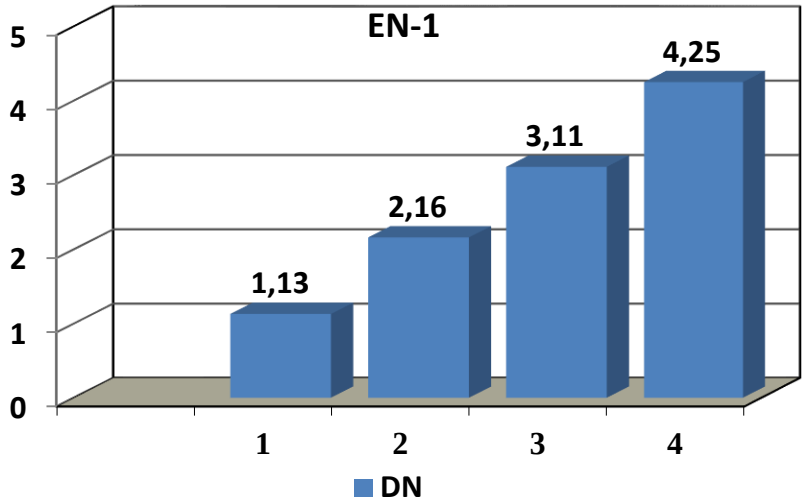


Figure 16. Comparison of EN-1 concentration in the blood at different stages of DN

When studying the level of NO in the blood of the examined patients, the level of NO in group 1 was determined as 24.8±2.37 μmol/l. The

NO concentration in group 2 was not statistically different compared to group 1 (p□0.05). A significant decrease in NO concentration was observed starting from group 3 and was at the level of 18.6±0.84 μmol/l. The NO concentration in all patients in this group was less than normal and differed from the 1st and 2nd groups by statistical significance, p1<0.05, p2<0.001, respectively.

In group 4, the NO level decreased almost 1.5 times from normal and amounted to 14.0±0.94 μmol/l (Table 1).

As can be seen from the results obtained, indicators reflecting the functional state of the endothelium have changed compared to earlier stages of DN (Fig. 17).

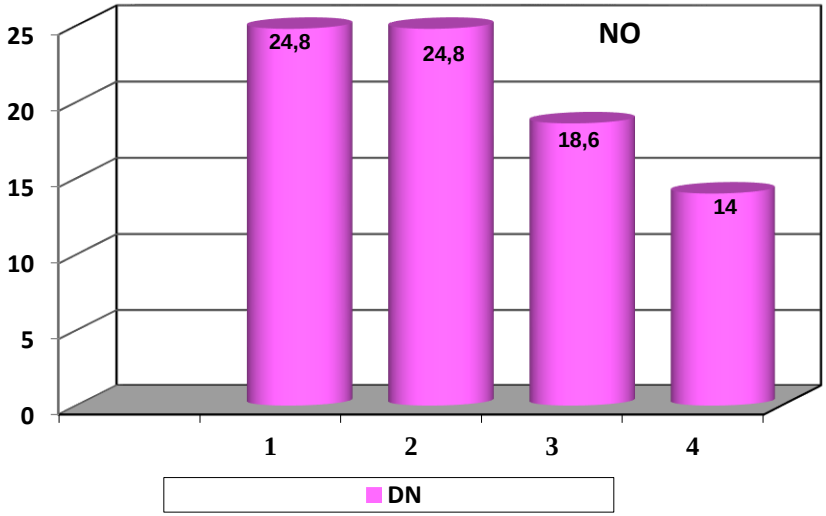


Figure 17. Comparison of NO concentration in the blood at different stages of DN

Depending on the stage of DN, one of the proliferative indicators of the endothelium, VEGF, was also studied in all 4 groups. It was noted that the level of this indicator increased starting from the 1st stage of DN. At stage 1 of DN, its concentration was high and amounted to

158.1±5.63 pg/ml. In group 2, this indicator was not statistically different compared to group 1 (p□0.05). An increase in this indicator was noted in each group depending on the stage of DN. A higher rate – 285.0±4.16 pg/ml is typical for group 4 (Table 1).

In stage 1 DN, the decrease in endothelial response averaged 11.40±0.34%. At the same time, in 12 patients, EDV was less than 10. As DN progressed, that is, as renal function decreased, a decrease in EIDV below 10% was also noted. (table 2). Thus, at the 2nd stage, EDV averaged 9.91±0.15%, at the 3rd stage 8.32±0.11%, and at the 4th stage 7.68±0.15%.

Table 2

EDV level in DN

	DN (n=120)			
	I n=30	II n=30	III n=30	III n=30
EDV %	11,40±0,34 (9,2–14,0)	9,91±0,15 (8,2–11,4) p_1<0,001	8,32±0,11 (7,2–9,0) p_1<0,001 p_2<0,001	7,68±0,15 (6,0–9,0) p_1<0,001 p_2<0,001 p_3<0,001

Note: P_1, P_2, P_3 – statistically significant difference compared to the indicators of groups 1, 2 and 3, respectively

Despite the fact that in the 2nd group there were cases when EDV was above 10%, in the 3rd and 4th groups all patients had EDV <10% (Figure 18). So, in the 2nd in 56.67%, in the 3rd and 4th in 100% of cases there was a violation of EDV.

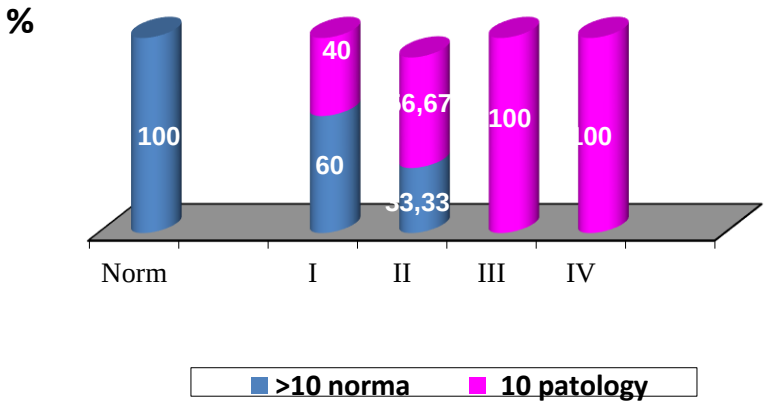


Figure 18. Frequency of changes in EDV at different stages of DN

In the 1st group, EIDV, averaging 12.59±0.09%, and in the 2nd group, respectively, 11.96±0.16%, meant a normal reaction (Table 3).

In DN, starting from the 3rd stage, EIDV was below 10% in 19 patients, while in the 4th group there was a significant decrease in this indicator in 29 patients. Thus, despite the fact that in group 3 the maximum EIDV was 11.4%, its average value was 10.03±0.11%. In the 4th group, there was one patient with EIDV above 10% and the average value was 8.86±0.10%.

Table 3.

EIDV depending on the stage of DN

	ДН (n=120)			
	I n=30	II n=30	III n=30	IV n=30
EIDV	12,59±0,09 (11,8–13,4)	11,96±0,16 (10,9–14,1) p_1<0,05	10,03±0,11 (9,3–11,4) p_1<0,001 p_2<0,001	8,86±0,10 (7,9–10,2) p_1<0,001 p_2<0,001 p_3<0,001

Note: P_1, P_2, P_3 – statistically significant difference compared to the indicators of groups 1, 2 and 3, respectively

At stages 1 and 2 of DN, all patients had EIDV of more than 10%. However, in subsequent stages 3 and 4, the frequency of violations increased sharply. So, if at the 3rd stage DN in the 3rd group in 11 patients (36.67%) EIDV was >10%, then in the 4th group in 29 patients (100%), EIDV was <10% (Figure 19)

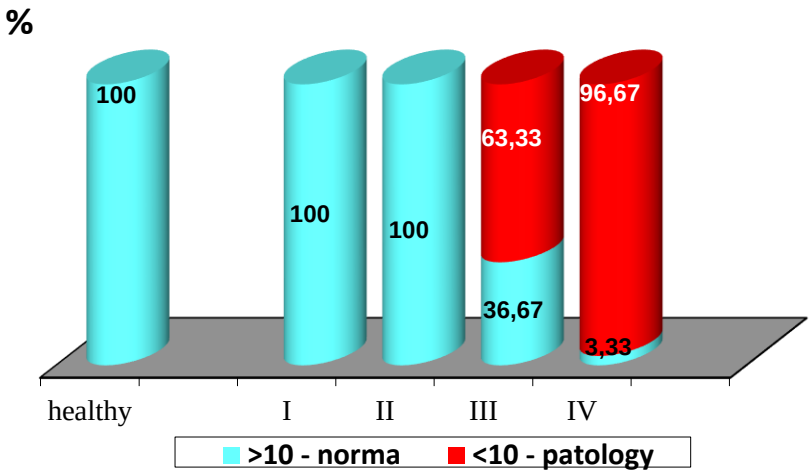


Figure 19. Frequency of changes in EIDV at different stages of DN

To assess the relationship between vasodilation and lipid spectrum in patients with DN, the presence and degree of dyslipoproteinemia were determined. In the groups, depending on the stage of DN, changes in the lipid spectrum were of different nature and frequency.

As DN progressed, there was a statistically significant difference in the level of total cholesterol (TC) between the groups and this indicator was significantly higher than the average values (Table 4).

Table 4.

Lipid spectrum indicators depending on the stage of DN

Indicators	DN n=120			
	1 n=30	2 n=30	3 n=30	4 n=30
TX, мг/дл	246,7±3,55 (195,0-284,0)	260,5±4,83 (200,0-301,0) p_1<0,05	288,6±6,91 (221,0-398,0) p_1<0,001 p_2<0,05	358,2±14,74 (221,0-641,0) p_1<0,001 p_2<0,001 p_3<0,001
TG, мг/дл	140,8±5,96 (60,0-173,0) (60,0-170,0)	163,7±5,60 (78,0-196,0) p_1<0,05	162,5±6,29 (90,0-201,0) p_1>0,05 p_2>0,05	197,4±9,19 (100,0-315,0) p_1<0,001 p_2<0,05 p_3<0,05
HDL, мг/дл	52,0±2,61 (28,0-77,0) (28,0-77,0)	39,4±1,02 (21,0-52,0) p_1<0,001	37,1±1,38 (24,0-50,0) p_1<0,001 p_2>0,05	33,3±1,04 (24,0-43,0) p_1<0,001 p_2<0,001 p_3<0,05
LDL, мг/дл	81,8±3,15 (46,0-107,0)	111,3±6,05 (64,0-193,0) p_1<0,001	139,2±5,79 (74,0-199,0) p_1<0,001 p_2>0,05	153,3±7,08 (82,0-229,0) p_1<0,001 p_2<0,005 p_3>0,05
AC	4,09±0,26 (1,9-7,9)	5,77±0,26 (4,1-11,6) p_1<0,001	7,1±0,34 (4,0-10,9) p_1<0,001 p_2>0,05	10,16±0,70 (5,6-25,7) p_1<0,001 p_2<0,001 p_3<0,05

P_1, P_2, P_3 – statistically significant difference compared to the indicator in groups 1, 2 and 3, respectively.

In group 2, the concentration of total cholesterol averaged 260.5±4.83 mg/dl and differed with statistical significance from group 1 ($p<0.05$). Despite the fact that this indicator was statistically significantly different in the 3rd and 4th groups, at the 4th stage its concentration increased significantly and amounted to 221.0 - 641.0 mg/dl. In contrast, an increase in the level of TG

concentration was noted at all stages of DN; only in group 4 the result obtained averaged 197.4 ± 9.19 mg/dl, thereby statistically significantly different from other groups (Table 4).

At all stages of DN, the levels of HDL and LDL were subject to changes. It is known that a decrease in HDL concentration is an independent risk factor for cardiovascular complications.

In group 1, the average HDL concentration was within the normal range. Despite this, in this group the minimum HDL value was 28.0 mg/dl. However, at subsequent stages of DN a significant decrease in this indicator was observed. Thus, in the 2nd group its concentration was 39.4 ± 1.02 mg/dl, in the 3rd group - 37.1 ± 1.38 mg/dl, in the 4th 33.3 ± 1.04 mg/dl.

In groups 2-4, corresponding to the stages of DN, there was an increase in LDL concentration. At this time, a statistically significant difference was revealed between the 1st and 2nd groups. Thus, in group 1 this figure was 81.8±3.15 mg/dl, in group 2 it was 111.3±6.05 mg/dl.

The atherogenic coefficient (AC) is an integral indicator and allows you to determine in advance with high accuracy the risk of developing atherosclerosis. However, in groups 2 and 4 there was a statistically significant difference in the KA indicator between the groups (Table 4). Thus, in the 2nd group this indicator was 5.77±0.26, in the 4th group it was 10.16±0.70.

If you pay attention, you can notice a significant increase in the risk of developing atherosclerosis in group 1 compared to the control group. In group 3, dyslipidemia was detected in the form of a statistical increase in total cholesterol and atherogenic lipoproteins.

Effect of the drug Glyciram on the functional state of the endothelium and kidneys at various stages of DN

During the study, each group was divided into 2 subgroups: subgroup A consisted of patients who received the drug glycyram along with classical treatment, subgroup B - patients who received treatment according to the DN treatment protocol. The study examined the effect

of the drug glycyram on endothelial and renal function. During treatment, a renoprotective effect, endothelial dysfunction and changes in the lipid spectrum were observed over a period of 3 months. 3 months after treatment, it was found that the creatinine level in these patients increased statistically significantly (Fig. 20). After treatment at stage 3 DN in subgroup 1A there were results with high reliability, and in subgroup 1B results with low reliability. At the 4th stage, a positive result was obtained in subgroup A, but in subgroup B this result was not obtained. Thus, in subgroup 4B, the creatinine level increased compared to its level before treatment (Fig. 20).

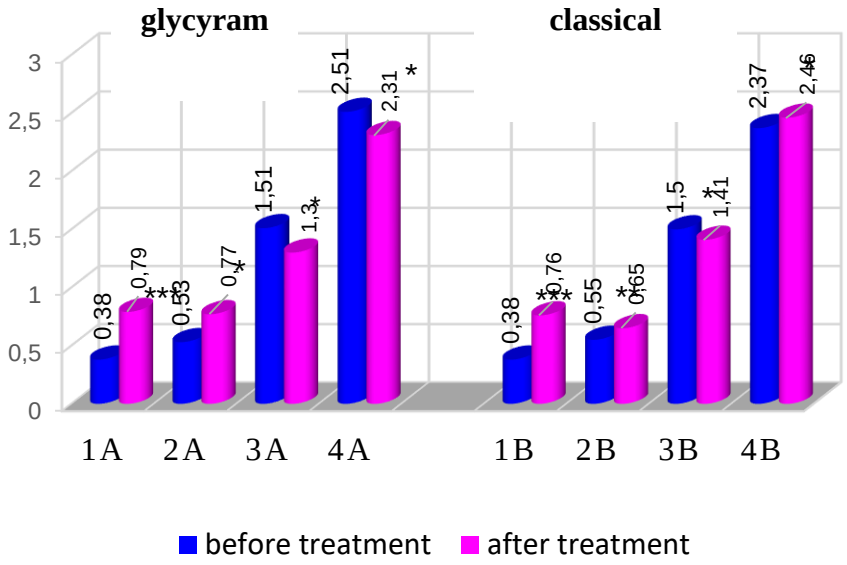
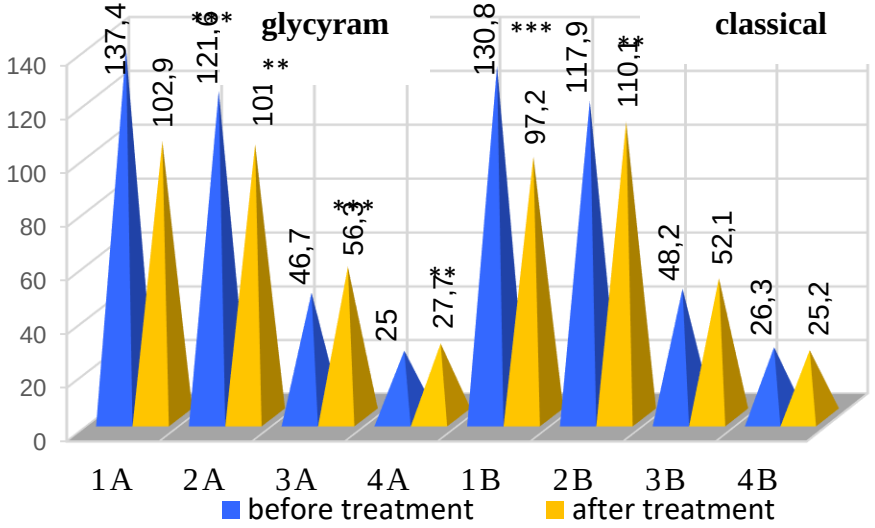


Figure 20. Blood creatinine level 3 months after treatment depending on the stage of DN.

Depending on the level of creatinine in the blood, the glomerular filtration rate (GFR) also underwent a statistically significant change in subgroups A 3 months after treatment (Fig. 21). Thus, in subgroup 1A it decreased by 4.5 ml/min/1.73 m2, in 2A - by 19.8 ml/min/1.73 m2, in

3A - by 9.6 ml/min/1.73 m2, in 4A - the decrease was to 2.7 ml/min. /1.73 m2. These changes were assessed as statistically significant.

However, in subgroup B, a statistically significant improvement was noted only at stages 1 and 2 of DN. Despite complex treatment, there was virtually no change in GFR at stages 3 and 4 of DN. (Fig. 21). Although its level decreased to 3.9 ml/min/m2 in subgroup 3B and to 1.0 ml/min/m2 in subgroup 4B, these changes were not determined to be statistically significant.



* - p<0.05; ** - p<0.01; *** - p<0.001

Figure 21. Dynamics of GFR during complex treatment

In addition to kidney function, 3 months after treatment, the state of the lipid spectrum in the blood was analyzed - the concentration of total cholesterol, TG, LDL, HDL, CA.

After 3 months of treatment, the average TC level decreased by 35.9% in subgroup 1A, by 38.8% in subgroup 2A, by 34.6% in subgroup 3A and by 38.4% in subgroup 4A. Despite the decrease in the

level of total cholesterol, in 2 patients in subgroup 3A and 4 patients in subgroup 4A, the result remained above normal (Fig. 22).

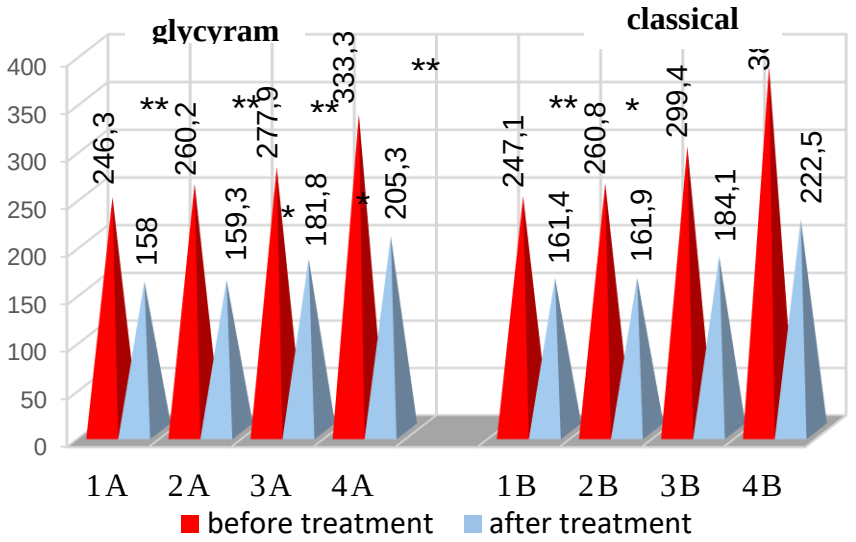


Figure 22. Changes in the concentration of total cholesterol in the blood during treatment with glycyram in patients with DN

As a result of treatment, after 3 months there was a decrease in TG concentration in the blood by 26.5% in subgroup 1A, 28.6% in subgroup 2A, 27.8% in subgroup 3A and 28.2% in subgroup 4A (Fig. 23) . However, TG levels were again high in 2 patients in subgroup 3A and in 9 patients in subgroup 4A. In subgroup 4A, on the contrary, an increase in TG concentration was observed in only 1 patient.

In DN, 3 months after treatment, the TG level decreased by 25.9% in subgroup 1B, by 22.8% in 2B, by 28.8% in 3B and by 28.3% in 4B. Although these patients had a decrease in the average TG concentration, this indicator was higher than normal in 2 patients in subgroup 3B and in 5 patients in subgroup 4B.

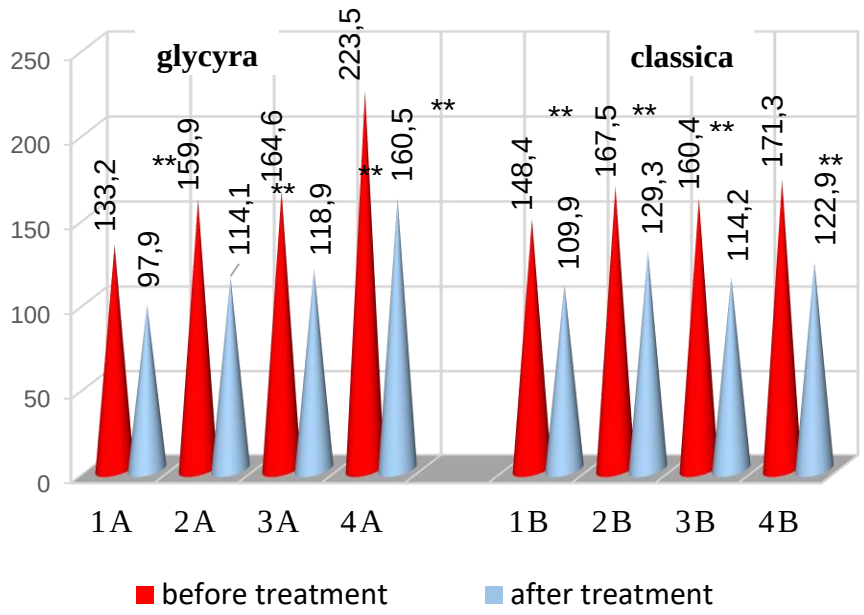


Figure 23. Changes in blood TG levels during glycyram treatment in patients with DN

In subgroup B, TC decreased by 34.7%, 37.2%, 38.5%, 41.9% in groups 1-4, respectively, and was statistically significantly different from the level before treatment ($p < 0.001$;). In subgroup 3B, 4 patients had a high level of total cholesterol. In subgroup 4B, the concentration of TC did not decrease to the target level and averaged 222.5±12.62 mg/dl. In this subgroup, only in 25% of cases the concentration of total cholesterol decreased to normal.

As noted above, the concentration of the endothelial dysfunction marker NO increased in all groups, starting from the 1st stage of DN before treatment (Fig. 24). The complex treatment performed improved the functional state of the kidneys and at the same time had a positive effect on endothelial function.

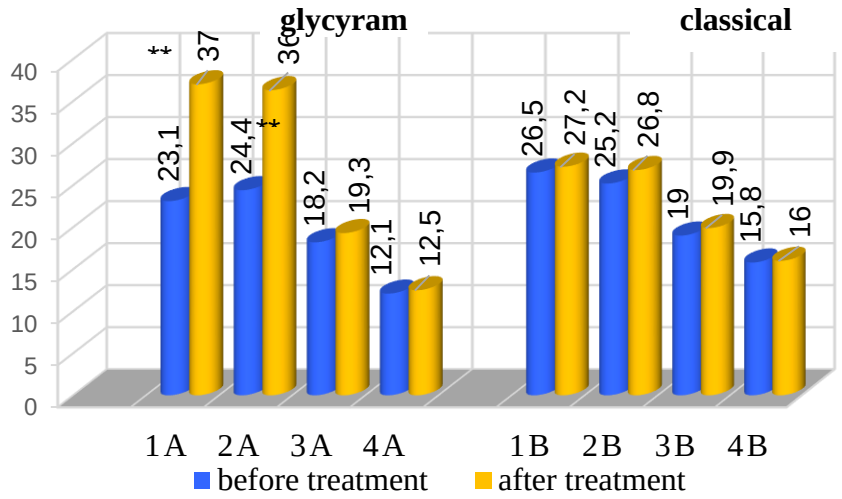


Figure 24 Changes in NO concentration in the blood during treatment for DN

3 months after complex treatment, the degree of change in EDV was determined in all patients. At this time, treatment results in both subgroups depended on the stage of DN.

When performing a test with reactive hyperemia, all patients after treatment in subgroup 1A had a normal EDV indicator. Normalization of the vasodilatory response was observed in 4 of 9 patients with reduced endoscopy in subgroup 2A 3 months after complex treatment. At stage 3 of DN, positive dynamics were observed in 3 patients in subgroup 3A after 3 months of treatment, but no improvement was noted in subgroup 4A. Thus, after treatment at stages 1-3 of DN, an increase in the degree of EDV was observed. In subgroup 1A it averaged 12.01%, in subgroup 2A - 11.0%. In subgroup 4A, treatment did not affect endothelial function. Thus, EDV in this subgroup was 7.7% (Fig. 25).

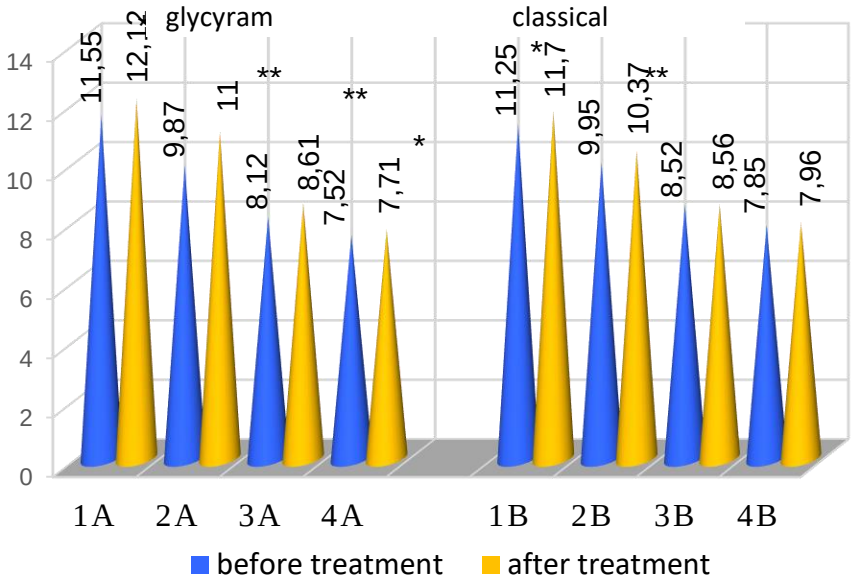


Figure 25. Dynamics of EDV depending on the stage of DN during complex treatment with glycyram

As can be seen from the figure, as a result of complex treatment, the vasodilation reaction of blood vessels at stages 1 and 2 in both subgroups reached a normal level, but in subgroup B in groups 3-4 it was not possible to obtain a reliable result by stage.

Thus, complex treatment with glycyram for 3 months led to positive changes in the vasodilation response of the vascular endothelium in patients, along with an improvement in the functional state of the kidneys. The effectiveness of treatment in both subgroups was different depending on the stage of DN. Thus, although at stages 1-3 of DN it was possible to obtain a positive clinical effect, at stage 4 of DN it was not possible to obtain a completely satisfactory result. The positive effect of treatment in individual analysis was higher at stages 1 and 2 of DN compared to stages 3 and 4.

CONCLUSIONS

1. In experimental diabetes, there is a pathogenetic relationship between endothelial dysfunction and disturbances in the processes of lipid peroxidation, cytokine status, functional activity of the liver, the CAF system and the composition of lipids in both the circulatory and lymphatic parts of humoral transport [1, 3, 5, 10, 13].
2. Changes in the lymphatic link are unidirectional with shifts in the circulatory link with some difference in the severity of changes in individual indicators of endothelial dysfunction LPO, cytokine status, functional activity of the liver, the CAF system and lipid composition [7, 18, 23, 25].
3. When modeling myocardial infarction against the background of experimental diabetes, there is a worsening of in ED, LPO, cytokine profile, liver enzyme activity, CAF system and lipid composition in both the blood and lymph. In parallel, there is a worsening of lymphatic drainage both at the organismal and organ levels [6, 9, 12].
4. Modeling of both occlusion of the artery of the lower limb against the background of experimental diabetes and occlusion of the renal artery against the background of experimental diabetes is also accompanied by aggravation of endothelial dysfunction in connection with disturbances in the processes of lipid peroxidation, cytokine status, functional activity of the liver, the CAF system and the composition of lipids in the blood, and the lymphatic links of humoral transport [2, 7, 8, 11].
5. Impaired lymphatic drainage of tissues, observed when modeling various vascular complications of diabetes (myocardial infarction, femoral artery occlusion and renal artery occlusion) is an important pathogenetic link that aggravates endothelial dysfunction in the circulatory link [2, 4, 11, 15].
6. The greatest disturbance in endothelial dysfunction in the pathogenetic relationship with changes in lipid peroxidation indicators, cytokine profile, liver enzyme activity, CAF system and

lipid composition in the blood and lymph according to severity is observed after simulating myocardial infarction, then occlusion of the renal artery and finally occlusion of the femoral artery against the background experimental diabetes [1 , 6, 22, 25].

7. The use of glycyram, which has a lymphotropic effect in case of occlusion of the renal artery against the background of experimental diabetes, prevents sharp disturbances in indicators of endothelial dysfunction, LPO, cytokine status, functional activity of the liver, the CAF system and the composition of lipids in the circulatory and lymphatic links [9, 28, 13].
8. In patients with DN, the degree of impairment of endothelial function in the blood depends on the stage of DN. The most significant changes are observed at stages 3-4, as evidenced by a significant increase in the concentration of En-1, VEGF with a parallel decrease in NO [9, 16, 17, 24].
9. In DN, a reduced vasodilation response was detected in 72% when studying EDV, and in EIDV - in 40% of patients. In addition, changes in the lipid spectrum, indicating acceleration of atherogenesis, are correlated with changes in EDV, which was not typical for EIDV [17, 26, 28].
10. The use of glycyram in the complex treatment of DN improves EDV and depends on the stage of the disease. The effectiveness of this therapy is also manifested in the positive effect [5, 13, 15, 18, 27].

PRACTICAL RECOMMENDATIONS

1. Regardless of the stage of DN, assessment of ED is important and for this purpose it is mandatory to determine the concentration of ED indicators (EN-1, VEGF, NO), as well as conduct an ultrasound examination of the brachial artery using the reactive hyperemia method.
2. In the clinic of this pathology, it should be taken into account that vascular disorders develop not only in the circulatory, but also in the lymphatic links.
3. Nephroprotective therapy in the early stages of DN allows normalizing vasoactive parameters of the vascular endothelium.
4. The inclusion of glycyram, which has a lymphatic effect, in the complex of well-known nephroprotective therapy for patients with DN prevents severe ED disorders and increases the effectiveness of their treatment.

List of scientific works published on the topic of the dissertation

1. Патогенетическое значение нарушения свертываемости крови и лимфы при экспериментальном сахарном диабете / Аллергология и иммунология, Сингапур, 2015, №3 том 16, стр.298 (соавт.: М.Х. Алиев, С.Д.Алиев, У.Д.Агамалиева, Ш.М. Гусейнова, С.И.Гаджиева, А.Ш.Гасымова).
2. К вопросу о патогенезе и патогенетическом лечении диабетической нефропатии // Азербайджанский Медицинский журнал, 2016, №2, стр.156-160.
3. Eksperimental şəkərli diabet zamanı oksidativ stress və immun tənzimləmənin pozulması/ Allergologiya,immunologiya və immunoreabilitasiya üzrə V Azərbaycan milli kongressi, Bakı, 2016, səh. 46 (həmmüəlliflər: Əliyev S.C., Əliyev M.X., Qasımova A.Ş., Əliyev E.M., Əliyev S.H., Şahverdiyev H.G.)
4. Дислипидемия и нарушения лимфатического дренажа тканей в патогенезе диабетической нефропатии // Азербайджанский Медицинский журнал, 2016, №4, стр. 90-94 (соавт.: Н.А.Джафарова, С.Д.Алиев, М.Х. Алиев, Э.М. Алиев)
5. Эндотелиальная дисфункция в патогенезе ангиопатии при сахарном диабете // “Sağlamlıq” jurnalı, 2016, №4, стр. 22-30.
6. Diabetik mikroangiopatiyaların patogenezində oksidativ stress və toxumaların limfadrenajının pozulması //“Sağlamlıq”jurnalı, 2016, №5, səh. 142-147 (həmmüəl: Qasımova A.S., Əliyev E.M., Əliyev O.S., Cəfərova N.Ə., Şahverdiyev H.G., Ağamalıyeva Ü.C., Bədəlova A.T.)
7. К вопросу о патогенетической терапии диабетической нефропатии (ДН) у больных сахарным диабетом (СД) второго типа // “Sağlamlıq” jurnalı, 2017, №1, стр. 82-86
8. Активация внутрисосудистого свертывания крови и лимфы в патогенезе кардиоваскулярных осложнений при сахарном диабете / Təbabətin aktual problemləri elmi –praktik konfrasın materialları, Bakı, 2017, səh. 98.
9. Влияние сулодексида на липидный состав и свертываемость лимфы при экспериментальном сахарном диабете /

Аллергология и иммунология, Москва, XXIV Всемирный конгресс по клинической медицине и иммунореабилитации, 2017, №4, том 18, стр. 242 (соавт.: М.Х. Алиев, С.И.Алиев, Ш.М.Гусейнова, В.Н.Гасимова,Л.Х.Сафаралиева).

10. Сулодексид в комплексной терапии больных диабетической нефропатией / Ə.Əliyevin anadan olmasının 120 illik yubileyi münasibəti ilə ATU-da keçirilən elmi-praktik konfransın materialları, Bakı, 2017, səh. 275-276. (həmmüəlliflər: Мурадова С.Р., Азизов В.А.)
11. Эндотелиальная дисфункция и лимфатический дренаж сердца при сахарном диабете // Азербайджанский Медицинский журнал, 2017, №, 61-65
12. Eksperimental şəkərli diabet zamanı lipid mübadiləsinin və limfanın damardaxili laxtalanmasının pozulması / Azərbaycan Cümhuriyyətinin 100 illik yubileyinə həsr olunmuş Təbabətin aktual problemləri adlı konfrans**,** Bakı, 2018, səh. 169 (həmmüəlliflər: M.X.Əliyev, S.H.Əliyev, Ş.M.Hüseynova, C.T.Əliyeva, L.X.Səfərəliyeva).
13. Diabetik angiopatiyaların patogenezində immun reaktivliyin və toxumaların limfadrenajının pozulmasının əhəmiyyəti // Azərbaycan Tibb Jurnalı, 2019, №2, səh. 74-79 (həmmüəl: Əliyev M.X., Əliyev O.S., Əliyev E.M., Ağamalıyeva Ü.C., Şahverdiyev H.G., Bədəlova A.T., Niftəliyeva S.F.)
14. Состояние биохимических почечных показателей и уровня протеинурии у больных сахарным диабетом и артериальной гипертензией / VI Евразийский конгресс кардиологов, Москва, 2018, стр. 21 (соавт.: В.А.Азизов, Ш.С.Ибрагимова, В.С.Мамедова).
15. Diabetik angiopatiyaların patogenezində limfa dövranı pozumasının damardaxili mexanizmlərinin rolu // Azərbaycan Tibb Jurnalı, 2019, №3, səh. 77-82 (həmmüəl: Əliyev M.X., Əliyev S.C., Əliyev E.M., Əliyev O.S., Ağamalıyeva Ü.C, Şahverdiyev H.G., Niftəliyeva, S.F. Bədəlova A.T.).
16. Tikanlı odotu(Phlomus pungeus Willd.) ekstraktının antidiabetik və limfotrop təsiriniin öyrənilməsi // Azərbaycan əczacılıq və

farmakoterapiya jurnalı, 2019, №1, səh. 33-36 (həmmüəlliflər Bədəlova A.T.,Niftəliyeva S.F., Ağamalıyeva Ü.C.,Şahverdiyev H.G.)

17. Lipidlərin peroksidləşməsinin və limfanın damardaxili laxtalanmasının fəallaşması diabetik mikroangiopatiyaların patogenetik mexanizmi kimi // Ə.T.Ağayevin 75 illiyinə həsr olunmuş konfransın materialları, 2019, səh. 90-93 (həmmüəlliflər: Əliyev S.C.,Hüseynova Ş.M., Əhmədzadə Ü.İ., Əliyeva C.T., Bədəlova A.T., Cəfərova N.Ə., Səfərəlyeva L.X. , Qasımova V.N.)
18. Эндотелиальная дисфункция и нарушение лимфатического дренажа тканей в патогенезе диабетической микроангиопатий // Патологическая физиология и экспериментальная терапия, 2020, №1 том 64, стр. 91-98 (соавт.: М.Х. Алиев, У.Д.Агамалиева, Ш.М Гусейнова, У.И.Ахмедзаде, Г.Г.Шахвердиев).
19. Эндотелиальная дисфункция и нарушение лимфатического дренажа сердца в патогенезе кардиоваскулярных осложнений сахарного диабета // Казанский медицинский журнал, 2020, №1 том 101, стр. 47-53 (соавт.: М.Х. Алиев , У.Д.Агамалиева, Г.Г.Шахвердиев, Д.Т.Алиева, С.И.Гаджиева)
20. Fibrinolytic lymphostimulation in treatment of diabetic angiopathies // Вестник хирургии Казахстана, Алматы, 2020, №3(64), стр. 22-28 (соавт.: Aliyev S.D., Aliyev M.Kh., Huseynova Sh.M., Ahmedzade U.I.).
21. Şəkərli diabt zamanı endotelial disfunksiyanın qan və limfanın damardaxili laxtalanmasında və toxumaların limfadrenajının pozulmasında rolu/ Professor Tamerlan Əliyevin 100 illiyinə həsr olunmuş "Təbabətin aktual problemləri-2021" mövzusunda beynəlxalq elmi-praktik kongressin materialları, 2021, səh. 322 (həmmüəlliflər: Ü.C.Ağamalıyeva. M.A.Pənahi, G.M.Sultanova, Ü.İ.Əhmədzadə).
22. Böyrəklərin xronik xəstəliyində müxtəlif mərhələlərində damar endotelinin funksiyasının qeyri-invaziv metodla

qiymətləndirilməsi // Azərbaycan Tibb Jurnalı, 2022, №1, 71-75 (həmmüəlliflər: İsmayılova Ş.Q., Məmmədova V.S., Ələkbərova A.K., Məmmədli S.M., Musayeva T.M.).

23. Взаимосвязь между показателями липидного обмена и эндотелиальной дисфункции на начальных стадиях хронической болезни почек // Медицинские новости Беларусь, 2022, №3 (330) март, стр. 73-76 (соавт.: Ш.Г.Исмайлова, Т.М.Мусаева, А.С.Рагимова, К.Ф.Маммедъярова, С.М.Маммедли).
24. The role of lipid metabolism in the development of endothelial dysfunction in diabetic nephropathy // World of medicine and biology Ukraine, 2023, №1(83), p. 126-130 (соавт.: Sh.G.Ismaylova).
25. Correlation of vascular endothelial function and inflammatory factors with renal function in patients with diabetic nephropathy // World of medicine and biology Ukraine, 2023, №3(85), p.129-133 (соавт.: Sh.G.Ismaylova, Ibrahimova Sh.S., Huseynova N.I.)
26. Evaluation of endothelial function in diabetic neprhopathy / (məruzə) International Paris Congress on Applied sciences, 2023,april 1-3, p. 176 (соавт.: Sh.G.Ismaylova, A.K.Alakbarova, A.S.Rahimova, S.M.Mammadli, N.I.Huseynova)
27. Effect of the glysyram on the functional state of the endothelium and kidney in diabetic nephropaty /(məruzə) 6-th İnternational Conference on medical and health sciences Mush,Turkey, 2023,march 04-06, p. 4 (соавт. Sh.G.Ismaylova, N.I.Huseynova, S.Muradova, T.M.Aliyeva).
28. Diabet nefropatiyası zamanı endotelin disfunksiyası / Zərifə Əliyevanın 90 iiliyinə həsr olunmuş konfransın materialları, Bakı, 2023, səh.79 (həmmüəlliflər: Ş.Q.İsmayılova, G.Ş.Şirəliyeva, F.Ə.İbadova).
29. Diabet nefropatiyası xəstələrində FGF-23-ün endotelin disfunksiyasının inkişafında rolu / Ümummilli lider Heydər Əliyevin anadan olmasının 100 illiyinə həsr olunmuş " Təbabətin aktual problemləri" Beynəlxalq elmi-praktiki kongressin materialları, 2023, səh. 197 (həmmüəlliflər:Ş.Q.İsmayılova).

LIST OF ABBREVIATIONS

aPPT	– Activated Partial Thromboplastin Time
AH	– Arterial hypertension
BA	– Brachial artery
CAF	– Coagulatin Anticoagulation Fibrinolisis
CRP	– C-Reactiv Protein
DM	– Diabetes Mellittus
DN	– Diabetic nephropathy
ED	– Endothelial Disfunction
EDV	– Endothelial dependent vasodilation
EIDV	– Endothelial independent vasodilation
EN-1	– Endothelin-1
EPGS	– End Products of Glycation
FAO	– Forms of Active Oxygen
GECs	– Glomerular Endothelial Cells
GFR	– Glomerular filtration Rate
HDL	– High-density Lipoprotein
IAM-1	– Intracellular Adhesion Molecules-1
IL-4	– Interleukin 4
IL-6	– Interleukin 6
LDL	– Low-density lipoprotrin
LFV	– Limph Flow Velocity
LPO	– Lipid Peroxidation
NO	– Nitrit oxyde
NOS	– Nitric Oxyde Synthase
NF-kB	– Nuclear factor-kB
TG	– Triglycerides
TNF-alpha	– Tissue necrosis factor-alpha
VAM-1	– Vascular Adhesion Molecule-1
VEGF	– Vascular Endothelial Growth Factor
VLDL	– Very low-density Lipoprotein
VWF	– Von Willebrand factor

The defense of the dissertation will take place "02 May" 2024 at "14" hours at the meeting BED 2.27/1 dissertation council, operating on the basis of the Azerbaijan Medical University

Address: AZ 1022, Baku, st. A. Gasimzade, 14 (administrative building of AMU, 2nd floor, conference hall.

The dissertation can be found in the library of the Azerbaijan Medical University.

The electronic version of the dissertation and the abstract is posted on the official website of the Azerbaijan Medical University (amu.edu.az)

The abstract was sent to the appropriate addresses «01» April 2024 year

Signed for print:27.03.2024
Paper format: 60x84 1/16
Volume: 77964 characters
Number of hard copies: 30