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ABSTRACT

of the dissertation submitted for the degree of
Doctor of Philosophy

IMPORTANCE OF EARLY DIAGNOSIS AND LYMPHATIC PHYTOTHERAPY IN THE TREATMENT OF DIABETES AND ITS COMPLICATIONS

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INTRODUCTION

Relevance and development of the topic.

Lower extremity circulatory disorders are one of the main causes of disability and mortality, as well as significantly reducing patients quality of life as a potential risk factor for amputation of the lower extremity or part of it as a dangerous complication of diabetes[1]. It was found that 70% of patients with diabetes (hereinafter DM) develop various complications, including micro- and macroangiopathies, neuropathy and osteoarthropathy on the background of ADHD and diabetic foot syndrome. In half of such patients, ADHD is complicated by the development of purulent-necrotic processes, 50-75% of which result in amputation at various levels. The frequency of amputations among DM patients is 17-45 times higher than among patients without DM[2]. After the first amputation, 30% of patients undergo amputation in the next 3 years, and up to 50% within 5 years. The average life expectancy of such patients is reduced to 5 years after amputation of one limb, and sharply reduced to one year after amputation of both limbs[3]. All this indicates that conservative treatment aimed at eliminating the possibility of amputation of the lower extremities in DM is still relevant, and requires a deeper study of the pathogenesis of CDLE and the development of new adequate treatment methods. It is known that autooxidation of glucose against the background of hyperglycemia during DM creates favorable conditions for disruption of lipid metabolism, activation of LPO and endothelial

[1] Gracheva, T.V., Levchik E.Yu. The quality of life of patients in the long term after surgical treatment of complicated forms of diabetic foot syndrome // Bulletin of Surgery. II Grekova, - 2010. Vol.169, № 3, - c. 29-33.

[2] Burleva, E.P., Babushkina Y.V., Galimzyanov F.V., Fominykh, A.N. Results of differentiated treatment of patients with diabetic foot syndrome at the stage of specialized surgical assistance // Surgery. Magazine N.I. Pirogova, -2019. №5, -c. 42-51. https://doi.org/10.17116/hirurgia201905142.

[3] Kuznetsov, E.V., Zhukova, L.A., Gulamov, A.A., Saenko, N.V. Medical and demographic characteristics of hospitalized patients with diabetic foot syndrome // Modern problems of science and education, -2016. №3 .; URL: http://www.science-education.ru/ ru / article / view? Id = 24774.

dysfunction[4,5]. The latter promotes the activation of intravascular coagulation, the development of macro- and microangiopathy by the passage of biologically active substances containing large amounts of vasoactive and procoagulants from the vascular wall into the blood[6,7].

In this case, special attention is paid to disorders at the level of microcirculation. As a result, the process of delivery of oxygen and nutrients to the lower tissues and the transport of toxic incomplete metabolic products from the intercellular space is disrupted, resulting in favorable conditions for the development of intoxication, edema and purulent-necrotic processes. Taking all this into account, some researchers recommend the inclusion of antioxidant and thrombolytic drugs in the prevention and treatment of ADHD. Although a number of advances have been made in the conservative treatment of CDLE due to research in this area, the number of amputations still cannot be reduced. All this makes the study of the problem in more depth and the early diagnosis of CDLE, in principle, the development of new methods of prevention and treatment one of the urgent problems of medicine[8,9,10,11].

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[4] Gerasimchuk, P.A., Kisil, P.V., Vlasenko, V.G., Pavlyshin AV Indicators of endothelial dysfunction in patients with diabetic foot syndrome // Bulletin RAMN, - 2014. № 5–6, - p. 107-111.

[5] Ketete, M, Cherqaoui R, Maqbool AR, Kwagyan J, Xu S, Randall O.S. Endothelial dysfunction: The contribution of diabetes mellitus to the risk factor burden in a high risk population. JBiSE, - 2013. 06 (06), - p.593-597. doi: 10.4236 / jbise.2013.66075.

[6] Biryukova, E.V., Shishkin, M.V. Diabetic microangiopathy: mechanisms of development, approaches to therapy // Clinical ophthalmology, - 2018. - №2, -p. 91-96.

[7] Ighodaro, O.M., Adeosun, A.M. Vascular complications in diabetes mellitus // Glob J Endocrinol Metab., - 2017. - №1 (2), - p.1–3.

[8] Levin, Yu.M. Basics of medical lymphology. M., Medicine, 1986, 287p.

[9] Mamedov, Y.D. Myocardial infarction. Lymphatic system of the heart. Pathophysiology and pathogenetic basis of treatment. M. Medicine, 1989, 220p.

[10] Aliev, S.D., Aliev, M.H., Gasymova A.Sh., Aliev, O.S., Aliev, E.M., Mamedzade, A.Ya., Agamalieva, U.D. Hemo- and lymphocoagulation component of impaired lymphatic tissue drainage in diabetes mellitus // Bulletin of Surgery of Kazakhstan, 2016, №4, p.17-20.

[11] Aliev, M.H., Aliev, S.D., Jafarova, N.A., Aliev, E.M., Aliev, O.S., Shahverdiev, G.G. Oxidative stress in the pathogenesis of microcirculation disorders in diabetes mellitus // Bulletin of Surgery of Kazakhstan, 2017, №1 (50), p.13-17.

In this sense, it is promising to study the role of disorders in the lymphatic system, which play an important role in the transport and detoxification of toxic products from the intercellular space in the body during DM, and to develop ways to eliminate them.

It is true that there is some information in the literature about the role of disorders of the lymphatic system in the development of diabetic lesions of the lower extremities and attempts to eliminate them, but these data are contradictory and do not study the problem.

The purpose of the study

In order to fulfill the goals and objectives of the research, clinical examinations were conducted in 35 patients and 10 clinically healthy people admitted to the Training and Surgery Clinic of AMU with the diagnosis of DM, and USDG of the lower extremities was performed. Experimental studies have been performed on laboratory animals in several areas.

During the study, DM and the occlusion of the femoral artery were modeled in experimental animals by injecting a 5% aqueous solution of alloxan monohydrate. For the examination, blood was taken from the external vein of the ear, and lymph was taken from the thoracic duct. Systemic indicators of LPO (DK, MDA and RG), lipid metabolism (HDLP, LDLP and VLDLP) and LAF in the blood and lymph are generally accepted studied by biochemical methods, lymphatic drainage properties of tissues were studied. The results obtained with figures are analyzed using modern statistical methods.

The purpose of the study - was to study the role of lipid metabolism, vascular coagulation of blood and lymph, as well as violation of lymphadrenage function of tissues in pathogenesis of ADP in rabbits with early diagnosis of CDLE in DM patients, experimental diabetes mellitus and unilateral occlusion of the femoral artery modeled.

Research objectives

1. To assess the potential of USDG in the early diagnosis of lower extremity circulatory disorders in patients with diabetes mellitus;
2. To study the indicators of intravascular coagulation, lipid metabolism and lipoperoxidation of blood and lymph in rabbits

with diabetes mellitus, as well as the lymphatic drainage function of tissues at the body level (control group II);

3. To study the indicators of intravascular coagulation, lipid metabolism and lipoperoxidation of blood and lymph during the modeling of unilateral occlusion of the femoral artery against the background of experimental diabetes, as well as lymphatic drainage function of tissues at the body level (control group III);
4. To study the effect of separate injection of emoxipin and urokinase with ADLC on rabbit coagulation, lipid metabolism and lipoperoxidation, as well as on the lymphatic drainage function of tissues at the body level in rabbits with diabetes mellitus;
5. To study the effect of concomitant administration of emoxipin, urokinase and ADLC in rabbits modeled on diabetes mellitus and unilateral occlusion of the femoral artery on the indicators of intravascular coagulation, lipid metabolism and lipoperoxidation, as well as lymphatic drainage function at the body level;

Research methods

In order to fulfill the goals and objectives of the research, clinical examinations were conducted in 35 patients and 10 clinically healthy people admitted to the Training and Surgery Clinic of AMU with the diagnosis of DM, and USDG of the lower extremities was performed. Experimental studies have been conducted in several areas. Thus, first of all, the effect of the preparatory measures important for the experiments on the indicators studied in the blood and lymph was studied (control group I). In the next stage, DM (group II control) was first modeled on rabbits to study the effect of femoral artery occlusion on blood and lymph parameters, as well as tissue lymphadenopathy function in experimental DM and against this background, and in other groups of rabbits on this background, femoral artery occlusion (control group III). modeled. In rabbits in the experimental group, first the antioxidant emoxipin and fibrinolytic urokinase were administered separately in combination with ADLC, and then the simultaneous administration of these

substances was performed both in experimental DM and in the background in blood and lymph. as well as the effect of tissues on lymphatic drainage.

In experimental animals, occlusion of the femoral artery was modeled by injecting a 5% aqueous solution of alloxan monohydrate into experimental animals and ligating the femoral artery. For the examination, blood was taken from the external vein of the ear, and lymph was taken from the thoracic duct. Systemic indicators of LPO (DC, MDA and RG), lipid metabolism (HDLP, LDLP and VLDLP) and LAF in the blood and lymph are generally accepted studied by biochemical methods. The results obtained with figures are analyzed using modern statistical methods.

The main provisions of the defense

- The results of experimental and clinical studies show that not only the thickness of the vessels, but also the violation of intravascular mechanisms play an important role in the disruption of blood circulation in the lower extremities during DM;
- Against the background of impaired lipid metabolism in experimental diabetes, LPO is activated in the blood as well as in the lymph, intravascular coagulation is enhanced and the lymphatic drainage function of the tissues is weakened;
- Modeling of unilateral occlusion of the femoral artery against the background of experimental diabetes leads to further deepening of the disorders detected in the blood and lymph, especially at the level of microcirculation, during experimental DM;
- Determination of lymphatic properties of emoxipin and urokinase separately in combination with ADLC allowed to eliminate not only blood but also lymphatic disorders in the simulation of unilateral occlusion of the femoral artery, both in experimental DM and against this background;
- Better therapeutic effect was observed in the combination of emoxipin, urokinase and ADLC in the modeling of both experimental DM and unilateral occlusion of the femoral artery on this background. Thus, not only disorders of lipid

metabolism and LPO in the blood, but also in the lymph were eliminated, intravascular coagulation was prevented, and most importantly, improvement of microcirculation was observed by the end of the study.

Better therapeutic effect was observed in the combination of emoxipin, urokinase and ADLC in the modeling of both experimental DM and unilateral occlusion of the femoral artery on this background. Thus, not only disorders of lipid metabolism and LPO in the blood, but also in the lymph were eliminated, intravascular coagulation was prevented, and most importantly, improvement of microcirculation was observed by the end of the study.

Scientific novelty of the research

Comparative aspects of intra-infrared dopolettography of lower extremities and unilateral occlusion of the femoral artery in the background of intravenous coagulation, lipid metabolism and lipoper-oxidation in the blood and lymph of simulated experimental animals, as well as lymphatic drainage function of tissues at the body level significantly expands our knowledge of the role of the lymphatic system in pathogenesis. It was found that in experimental DM, as in the blood, the process of free radicalization is activated in the lymph against the background of dyslipidemia, the concentration of LPO products increases and signs of endothelial dysfunction appear, resulting in increased intravascular coagulation and impaired microcirculatory circulation. The latter manifests itself with a weakening of the LFR from the lymph flow in the breast.

Modeling of unilateral occlusion of the femoral artery against the background of experimental DM, ie disruption of blood flow in the main artery, leads to a deepening of the changes found not only in the blood, but also in the lymph, especially microcirculation. A comparative analysis of the results of the study shows that oxidative stress, endothelial dysfunction and activation of intravascular coagulation in chronic hyperglycemia (as is known from the literature) play an important role not only in microhemocirculation, but also in microcirculatory disorders.

For the first time, emoxipin and urokinase, which are widely

used in practical medicine and have different mechanisms of action, as well as a collection of plants derived from the flora of Azerbaijan and made of plants with different mechanisms of action, were found to have lymphatic properties. Thus, the use of drugs used in the modeling of experimental DM and unilateral occlusion of the femoral artery in this background has a positive effect not only on the studied LM, LPO and intravascular coagulation in the blood but also in the lymph, significantly improves microcirculation. A more effective therapeutic effect was observed when co-administered emoxipin and urokinase with ADLY, which may affect various mechanisms of vascular complications of DM. This prevents long-term activation of LPO and intravascular coagulation, not only in the blood but also in the lymph, and most importantly, LFR maintains its superior position from the breast to the end of the study, especially in the control group.

Theoretical and practical significance of the research

Activation of LPO and intravascular coagulation in the lymph, as well as in the blood during the modeling of experimental DM and unilateral occlusion of the femoral artery on this background, is accompanied by impaired microcirculatory circulation. Accumulation of toxic metabolic products in the intercellular space as a result of the formation and difficulty of transport of the latter lymph creates favorable conditions for the development of intoxication, edema and, consequently, purulent-necrotic processes. All this creates a pathogenetic basis for the development of ways to eliminate not only blood but also lymphatic disorders. In this sense, the discovery of the lymphatic properties of emoxipin and urokinase in combination with ADLC, which may affect various pathogenetic mechanisms of CDLE, opens up a wide range of possibilities to eliminate lymphatic disorders in patients with CDLE in the background of DM. The results of studies on experimental animals leave no doubt as to the accuracy of this assumption. Thus, in our studies of animals with experimental DM and unilateral occlusion of

the femoral artery in this background, the combined use of emoxipin and urokinase separately with ADLC not only in the blood but also in the lymph, eliminating disorders of lipid metabolism and LPO, prevention of intravascular coagulation. The main thing is to improve microcirculation by the end of the study. A more rational therapeutic effect was observed with the combined use of emoxipin, urokinase and ADLC.

Applying of work results in practice

The results of the study are used in lectures and practical classes at the Department of Pathological Physiology of the Azerbaijan Medical University.

Approbation and application

Separate fragments of the dissertation were presented at the XXII International Congress on Rehabilitation and Immunorehabilitation in Medicine (Singapore, 2015), V Azerbaijan National Conference on Allergology, Immunology and Immunorehabilitation (Baku, 2016), scientific-practical conference dedicated to the 120th anniversary of Aliyev. (Baku, 2017), at the Final Scientific Conference of AMU (Baku, 2017), at the XXII Republican Scientific Conference of Doctoral Students and Young Researchers (Baku, 2019), as well as at the initial interdepartmental discussion (08.07.2021, protocol № 2) and FD of AMU 03.013 Report and discussion at the seminar of the Approbation Council organized under the Dissertation Council (28.04.2022, protocol №4).

13 scientific works on the topic of the dissertation were published. 7 of them were published in the publications recommended by the EAC under the President of the Republic of Azerbaijan, including 5 articles in the publications included in the international indexing and summary databases, and 5 are theses. 1 of the theses was published abroad, and 4 in the materials of international and national congresses and conferences and 1 patent.

Name of the organization where the dissertation work is carried out

The dissertation work was carried out according to the plan of scientific-research work of the Department of Pathological Physiology of the Azerbaijan Medical University and the Teaching Surgery Clinic .

The total volume of the dissertation with a sign, indicating the volume of the structural units of the dissertation separately.

The structure and scope of the dissertation. The dissertation is written in 187 pages in the Azerbaijani language, from the introduction (9 pages, 15572 signs), literature review (16 pages, 32106 signs), materials and methods (15 pages, 17850 signs), Chapter 3 from personal research (16 pages, 20131 signs) , Chapter 4 (30 pages, 38420 characters), Chapter 5 (33 pages, 44765 characters), Chapter 6 (32 pages, 42282 characters), results (2 pages, 3561 characters), practical recommendations (1 page, 776 characters) (total 215463 characters). The dissertation consists of a list of 215 literature sources. Of these sources, 2 were used by local authors, 137 by Russian authors, and 76 by English authors. Visualized with 35 tables and 14 figures.

The main content of the dissertation

In the introductory part of the dissertation, the relevance of the research work is substantiated, goals and objectives are defined, scientific novelty and practical significance are given, the main provisions submitted for defense are indicated, information on approbation, scope and structure is included.

In the first chapter, the works of domestic and foreign authors on the role of DM and its complications, as well as the role of oxidative stress, disruption of lipid metabolism and hemostasis in the pathogenesis of CDLE, were widely commented, analyzed and summarized. Extensive analysis of statistical data on the prevalence, amputation, death and disability of the mother of patients with DM, the development of oxidative stress in the background of chronic hyperglycemia, endothelial dysfunction and hemostasis played an

important role in the development of both DM and its purulent-necrotic complications. Given all this and the inability of modern insulin therapy to prevent complications of DM, especially delayed vascular complications, some researchers suggest that the treatment should include antioxidants and antithrombotic drugs. However, the failure of the research conducted in this direction also yielded the expected results, which led to the conclusion that a more in-depth study of the pathogenesis of CDLE. These have led to the study of the role of the lymphatic system, which performs a number of important functions in the body, in the pathogenesis of CDLE during DM and the development of adequate lymphatic correction methods.

The second chapter provides research materials and methods. In the clinical part of the study, lower extremity USDG was performed in 35 DM patients and 10 clinically healthy individuals. The experimental part of the study was performed on 128 rabbits of the genus Chinchilla weighing 2.0-3.5 kg. The experiments on rabbits were carried out in accordance with the requirements of the European Convention for the Protection of Vertebrates and Directive 86/609 / EEC. Thus, all the surgeries necessary to remove lymph from the breast for analysis were performed under anesthesia. For this purpose, solutions of ketamine (8 mg / kg) and diphenhydramine (0.15 ml / kg of 1% solution) were injected into the external vein of the ears of experimental rabbits. In our study, experimental SD was modeled in 114 rabbits by intravenous administration of a 5% aqueous solution of alloxan monohydrate at a dose of 100 mg / kg. All laboratory animals were divided into control and experimental groups. The effect of preparatory measures (fixation, analgesia, surgery, etc.) on the indicators studied in the blood and lymph of 14 rabbits included in the control group was studied.

For the examination, blood was drawn from the rabbit's ear vein and lymph from the breast. Kornienko et al. (1977) [12] to the method of M.Kh. Aliyev, V.Q. Based on Mammadov's (1990)

[12] Kornienko, A.A., Kulikovsky, N.N., Sorokaty, A.E. Topical issues of topographic anatomy and operative surgery. M., 1977, vp.1, p.22-13.

modification, intravenous blood and lymph coagulation, lipid content, and LPO were studied before, during, and 5, 15, 30, 60, and 90 days after alloxan injection, using commonly accepted biochemical methods.

The lymphatic drainage function of the tissues was assessed by determining LFR from the thoracic duct. LFR from breast milk was determined based on the amount of lymph collected from breast milk in ml per unit time per kg of body weight of the rabbit. (min. ml / kg). 19 head of rabbits were included in each of the control subgroups, in which the DM model II was created and on this background the unilateral occlusion of the femoral artery was modeled III. The animals of the experimental group, in turn, were divided into 4 subgroups, each with 19 rabbits. In the experimental series, the effects of individual and combined injection of emoxipin and urokinase on the studied parameters in the blood and lymph, as well as the lymphatic drainage properties of tissues were studied in rabbits modeled on experimental DM and unilateral occlusion of the femoral artery.

All figures obtained as a result of the study were statistically processed with the help of EXCEL and STATISTICS software packages based on Student and Wilcoxon methods, using parametric and non-parametric methods, taking into account modern recommendations.

In the third chapter, USDG examinations were performed in 35 DM patients and in the lower extremities of 10 clinically healthy individuals. 15 (42.8%) of the examined patients were men, 20 (57.1%) were women, and 4 (40.0%) men and 6 (60.0%) women were included in the control group.

16 of the examined patients were diagnosed with insulin-dependent and 19 with insulin-dependent DM. According to Anamnesis data, the duration of the DM lasted for patients in 5 to 1 year, in 10-1 to 5 years, in 11-6 to 10 years, and in 9-more than 10 years. Of the patients involved in the study, those aged 50 to 64 years were the majority - 22 (62.8%).

The shoulder-ankle index, an important diagnostic criterion in patients, was assessed during the USDG examination. It should be

noted that ShAI (shoulder ankle index) is a reliable method of assessing arterial occlusion and is considered the gold standard for screening and diagnosis of peripheral arterial occlusion lesions. The normal range is 0.90-1.30 in adults. Below 0.8 indicates peripheral arterial disorders and is important as a prognostic criterion for gangrenous changes in patients with lower (<0.05) levels.

In DM patients, this criterion is slightly different. Given that arterial occlusion is associated with medicclerosis, this group of patients has higher blood pressure and a median sclerosis of more than 1.3. Such indicators can be observed in patients with chronic renal failure.

In the study, SHAI in the right and left legs in patients with DM was 1.09 ± 0.14 and 1.2 ± 0.18, respectively. There was no significant difference in this indicator in the control group.

The study did not show any occlusion disorders in the vascular network in group I patients. In 3 patients from this group, the FDI was high, 1.5-1.7, and hemodynamically significant stenoses were found in the distal segments of the cane arteries and in the carotid arteries. No stenotic changes were observed in group II patients. In group III patients,ShAI was higher in 5 patients and vascular occlusion was observed.

The fourth chapter is devoted to the interpretation of the results of studies conducted on 52 rabbits included in the control group. Laboratory animals included in the control group were divided into 3 subgroups. In 14 rabbits included in the first control subgroup, saline solution was injected instead of 5% aqueous solution of alloxan monohydrate and the effect of preparatory measures on the studied parameters was studied. As a result of the research, it was found that the changes detected in the blood and lymph during the preparatory measures were not sustainable, ie the indicators returned to normal levels in a short time.

Modeling of experimental DM in 19 rabbits in control group II caused profound changes in the blood as well as in the lymph. Thus, although there is a tendency to change the direction of hypocoagulation in both humoral environments (blood and lymph) from the very first stages of the study, there are changes in the

direction of acute hypercoagulation from the 15th, especially the 30th day of the study. From the 15th day of the study, hypercoagulation begins to develop in the blood. Indicators such as DPAT, PD and TD are reduced in the blood by 13.4%, 12.8% and 20.7%, respectively, and in the lymph by 27.8%, 29.8%, 34.6%, respectively, VF, FP and the level of AT-III in the blood increases by 42.6%, 35.0% and 28.4%, respectively, and in the lymph by 47.2%, 28.3% and 31.2%, respectively ($p < 0.05$-0.001). Towards the end of the study, the changes in the direction of hypercoagulation gradually deepened to 30 (TD decreased to 69.1% of normal level) and 60 days (PD and INR to 69.1%, respectively, 65.8% of the corresponding normal). and decreased to 65.4%, while the level of VF exceeded the normal level by 68.7%) reached its peak ($p <0.001$). In the later stages of the study, changes in the direction of hypercoagulation begin to weaken on some indicators. However, the risk of thrombosis in the blood and lymph remains until the end of the study. Thus, VF, FDP, markers of intravascular coagulation, are clearly identified in both systems by the end of the study. At the same time, there are significant changes in the lymphatic drainage function of the tissues, although LFR from the thoracic duct increases slightly at the beginning of the study, weakens with prolongation of the study and decreases to 55.6% of the norm by the end of the study ($p <0.001$). Modeling of DM in rabbits also had a significant effect on lipid metabolism. Thus, the amount of atherogenic lipids in both blood and lymph increased, and LPO became significantly more active. Such changes are usually observed from the 15th day of the study. During this period of study, HDLP in the blood decreased to 76.5% of the norm, and in the emphysema to 89.4%, while the amount of LDLP and VLDLP in the blood was 63.6% and 46.3%, respectively, and in the lymph, 20.0% and 24.4%, respectively ($p <0.001$). Activation of LPO began on the 7th day of the study. As the study period progresses, the LPO intensifies and reaches its maximum level by the 30th day of the study. Thus, the level of DC and MDA in the blood increased to the maximum and exceeded the norm in the blood by 3.7 and 2.0 times, respectively, and in the lymph - by 2.7 times and 93.9% ($p <0.001$). All of these were accompanied by a decrease in RGin both blood and

lymph from day 30 of the study ($p < 0.001$). Thus, the creation of the DM model in rabbits leads to the activation of intravascular coagulation not only in the blood but also in the lymph[13,14] an increase in the amount of atherogenic lipids, activation of LPO and weakening of lymphatic drainage of tissues[15,16].

In 19 rabbits included in control group III, unilateral occlusion of the lower extremities was modeled against the background of experimental DM. The results of the study show that the changes in the direction of hypercoagulation found in the blood and lymph during experimental DM are further deepened. Such changes were recorded from the 15th day of the study. When comparing the obtained changes with the control group indicators, markers of activation of intravascular coagulation in the blood and lymph were found to be more visible, and this difference between the changes decreased with the length of the study, but by the end of the study, changes in the direction of hypercoagulation, i.e., the risk of thrombolysis, were preserved both in the blood and lymph. At the same time, the amount of atherogenic lipids in the blood and lymph significantly increased, exceeded the control group, and LPO became more active. This can be seen when comparing the concentrations of HDLP in the blood and lymph. For example, on the 60th day of the study, the amount of HDLP in the blood decreased to 45.1% of the

[13] Dzugkoev, S.G., Khetagurova, L.G. The role of changes in the associated system of peroxidation of lipids, antioxidant protection, microcirculation and hemostasis in the pathogenesis of diabetic angiopathy // Bulletin of new medical technologies, - 2008. - №1, - p. 40-41.

[14] Rodin, A.N., Zakhvatov, A.N., Belyaev, A.N., Tarasova, T.V., Zakharkin, I.A. Effectiveness of regional pharmacotherapy in the complex treatment of necrotic-necrotic complications of diabetes // Modern problems of science and education, - 2017. - № 5.; URL: http://www.science-education.ru/ru/article/view?id= 26808.

[15] Nekrasova, E.G., Dubensky, V.V., Miller, D.A. Features of vascular hemostasis associated with diabetes mellitus in patients with stop mycoses, and their treatment with correction of microcirculatory disorders // Immunopathology, allergy, infectious disease, - 2011. - №2, - p. 53-62.

[16] Vasiliev, P.V., Shishkin, A.N., Erofeev, N.P., Bubnova, N.A., Pchelin, I.Yu. Non-invasive assessment of microcirculation in patients with late complications of type 2 diabetes // Regional blood circulation and microcirculation, - 2015. -№14, - c. 28-33.

baseline, but in the lymph it was 36.5%. In addition, on the 60th day of the study, the level of LDLP in the blood exceeded the norm by 2.47 times, while the increase in lymph was 2.54 times ($p < 0.001$). Quantitative differences of the same nature can be observed when comparing the amount of VDLLP in the blood and lymph. Such differences in the lipid content of blood and lymph can be found at any stage of the study. However, it should be noted that the direction of change was the same at all stages of the study in both systems. Similar changes can be seen when comparing LPO levels in the blood and lymph. It should be noted that unilateral occlusion of the femoral artery against the background of experimental DM is accompanied by more intensive activation of LPO. That is, although the amount of LPO products increases in both blood and lymph, there are quantitative differences. Thus, the amount of DC in the blood (on the 15th day of the study was 64.4% of the baseline level 2.43 times higher than normal, and in the lymph this indicator was 62.7% ($p < 0.001$).

Thus, our studies have shown that in the context of oxidative stress in chronic hyperglycemia, along with blood, increased intravascular coagulation of lymph and increased risk of thrombosis play an important role in the disruption of lymphatic drainage of tissues during experimental DM. Unilateral occlusion of the femoral artery against the background of experimental DM leads to a deepening of these changes. The latter is fully consistent with the literature [17] on the reduction of lymph transport from the lower extremities to 64.7% in the initial phase of DPS. All of this provided a pathogenetic basis for the subsequent administration of antioxidant emoxipin and fibrinolytic urokinase to experimental animals separately and in combination with ADLC.

In the fifth chapter, the effects of emoxipin and urokinase on blood and lymph parameters studied separately with ADLC in experimental DM were studied. Emoxipin was used in combination with ADLC in the treatment of 19 rabbits in the experimental group.

[17] Shevchova, E.V. Impairment of microcirculation and blood-lymph circulation in the lower extremities of patients with the initial stage of diabetic foot syndrome and their correction. Diss. k.m.n., Novosibirsk, 2009, 147p.

Studies have shown that in this group of experimental animals there are changes in the direction of hypocoagulation not only in the blood but also in the lymph. Thus, indicators such as DPAT, PD and TD in the blood and lymph begin to decline from the very first days of the study. Although the direction of the changes is the same in the blood and lymph, there are also quantitative differences. For example, although HFTM was superior in the blood for 60 days compared to both the baseline and the corresponding control group, such dynamics in the lymph continued for a total of 15 days. That is, on day 30, was reduced to baseline in the blood, but was superior to the control group. Although the dynamics were repeated on day 60 of the study, at the end of the study, this indicator decreased again to 74.5% of the baseline, but did not differ from the control group. Indicators such as PD, TD underwent changes in the direction of similar hypocoagulation. At the same time, the anti-thrombotic system was activated. All this indicates a significant reduction in intravascular coagulation of blood and lymph during the combined treatment of experimental DM with emoxipin and ADLC, and that emoxipin and ADLC have both anticoagulant effects. Such treatment also had a beneficial effect on the lymphatic drainage properties of tissues. This is manifested, first of all, by an increase in LRF from the breast. Compared to the baseline, this increase was more than 2.3 times on the 15th day of the study ($p < 0.001$). Compared to the control group, the dynamics of the changes were slightly different at first (day 15 of the 15th study), but then, ie from the 60th day until the end, they did not differ from the control group. Although LFR from breast discharge began to decline in the later stages compared to the baseline, it was able to maintain its advantage until the end of the study ($p < 0.01$). Thus, studies have shown that such treatment not only reduces the intravascular coagulation of lymph, but also increases the LRF from the breast, ie improves lymphatic drainage of tissues. Co-administration of emoxipin and ADLC also has a positive effect on the lipid composition of blood and lymph. In this case, the amount of atherogenic lipids in both systems is significantly reduced and the LPO is weakened. HDLP increases more intensively in the blood (on the 60th day of the study, this increase was 2.3 times

compared to the baseline, and 5.3 times compared to the control group), and in the lymph, these changes were slightly weaker (compared to the baseline). 66.7% on day 15 and 2.9 times on day 60 of the study compared to the relevant control group) ($p < 0.001$). QSH was higher in the blood on the 30th day of the study (27.8%) than in the baseline, on the 15th day of the study in the lymph (33.3%), and on the 30th day of the study in the blood compared to the control group (2.2). times), and in the lymph increased on the 60th day of the study (78.1%) ($p < 0.05$-0.001). Thus, the study found that co-treatment of emoxipin of experimental DM with ADLC also had a beneficial effect on blood and lymph lipid composition and LPO. The amount of atherogenic lipids in the blood and lymph is significantly reduced, and LPO is significantly weakened. The anticoagulant effect of emoxipin and ADLC is primarily explained by the interaction between oxidative stress and hemostasis that develop during DM [18, 19]. Our studies have shown that such a connection also exists in the lymph. Thus, the combined administration of emoxipin and ADLC in experimental DM slows down the intravascular coagulation of not only the blood but also the lymph.

At the same time, improvement of lymphadrenage of tissues once again confirms the important role of the underlying system in the transport of humoral transport in the direction of blood-interstitial fluid and lymph, and improvement of microhemocirculation not only as a result of weakening of blood intravascular coagulation, but also improvement of microlimphasirculation against the background of slowing of intravascular coagulation of lymph[20]. Injecting urokinase during experimental DM caused profound changes in blood and lymph parameters. Although some differences between the changes

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found in the blood and lymph were noted, the direction of the changes was largely the same. That is, co-administration of urokinase with ADLC in experimental DM weakens not only the blood but also the lymphatic clotting of the lymph and increases the fibrinolytic activity in both systems. However, it is important to note that although FF activity increased more intensively in the blood than in the early stages of the study, in the later stages of the study, ie as the study period progressed, the predominance shifted to the lymph and the FF in the lymph increased more intensively. Comparison of other indicators also shows that the differences are mainly quantitative. For example, although DPAT in urokinase treatment with ADLC in both systems (blood and lymph) exceeded the baseline and control group values at the maximum level on day 30 of the study, this advantage was 71.1% and 2.0 times in the blood, respectively. lymph (30.0% and 85.8%, respectively). When comparing the PD, it becomes clear that the difference is somewhat different. In other words, if the PD increased in the blood and reached its maximum on the 15th day of the study, and this increase was 64.4% and 2.2 times, respectively (assuming baseline and control group indicators), this indicator in the lymph reached its maximum on the 15th day of the study. day and was 75.7% and 2.5 times higher, respectively ($p<0.001$). Comparison of TM in blood and lymph shows that although the direction of changes is the same, other differences are formed in blood and lymph. For example, although TD changes in the blood only on days 15 and 30, it is possible to see changes in the direction of hypocoagulation in the lymph at almost all stages of the study. One of the notable changes is that the level of VF (Villebrand factor) in both systems is much lower than in the respective control group, rather than in the respective baseline. Such dynamics were observed in both blood and lymph until the end of the study. Antimicrobial system parameters also increased in both fluids, and this was more pronounced in the lymph than in the blood. Thus, the weakening of intravascular coagulation in both systems is confirmed by the fact that the markers of activation of intravascular coagulation are not visible in the blood or lymph for a long time.

Co-administration of urokinase and ADLC also had a benefi-

cial effect on blood and lymph lipid composition, reducing the amount of atherogenic lipids and significantly reducing the intensity of LPO. The latter is manifested by a decrease in LPO production in both blood and lymph and an increase in RG. Although the direction of the detected changes is the same, some differences are noteworthy. This can be verified by comparing the dynamics of change of any indicator at any stage. For example, the lowest level of DC in the blood of LPO products (decreased to 47.1% of the control group) on the 30th day of the study, and the lowest level of MDA (decreased to 54.4% of the control group). lymph was recorded on day 30 of the study ($p < 0.001$). Although the amount of RG increased in both systems and reached a maximum on day 60 of the study in both systems, it was quantitatively different. Thus, at this stage of the study, RG exceeded the control group in the blood by 72.4%, and in the lymph - by 65.6% ($p < 0.001$). When we compare the indicators of lipid metabolism in the blood and lymph, we see that the direction of changes is the same, but there are also quantitative differences. That is, the amount of atherogenic lipids in both systems decreases, and against this background, the amount of HDLP increases. Thus, the maximum on the 30th day of the study in both systems (79.7% and 71.6%, respectively) compared to the baseline HDLP, and on the 60th day of the study compared to the control group (3.4 times, respectively and 3.6 times) ($p < 0.001$). Similar and different dynamics can be observed in the dynamics of atherogenic lipids. For example, although LDLP levels fell to the lowest level in both systems on day 60 of the study, the rate was 30.5% in the blood and 30.4% in the lymph ($p < 0.001$). All this is an important condition for the prevention of vascular complications in DM and opens new opportunities for the use of urokinase and ADLC to prevent the development of complications in DM.

In rabbits in the sixth chapter, emoxipin and urokinase were injected in combination with ADLC. At this time, intravascular coagulation in the blood and lymph began to weaken from the first stage of the study. However, the rate of change was different. For example, although DPAT was superior in the blood for 60 days compared to both the baseline and the corresponding control group,

such dynamics in the lymph continued for a total of 15 days. That is, on day 30, DPAT was reduced to baseline in the blood, but was superior to the control group. Although the dynamics observed in the early stages of the study were repeated on the 60th day of the study, at the end of the study, this indicator decreased again to 74.5% of the baseline, but did not differ from the control group. Although the PD has undergone similar changes, some differences are also noteworthy. Thus, PD in the blood significantly exceeded both the initial and the corresponding control group by the end of the study, but such dynamics in the lymph was observed until the 60th day of the study. That is, the PD was reduced to the level of the initial and appropriate control group by the end of the study. The change dynamics of TD was also different. That is, the TD index in the blood and lymph exceeded both levels (baseline and control group) by the end of the study. In the direction of hypocoagulation, TT was recorded on the 30th day of the study in both blood and lymph, on the 30th day of the study in the blood compared to the control group, and on the 15th day of the study in the lymph. Similar changes can be seen when comparing VF in the blood and lymph. That is, although VF in lymph did not differ from the baseline at the end of the study, it was less than in the control group by the end of the study ($p < 0.05$-001). Co-administration of emoxipin with urokinase and ADLC also activated the antithrombotic system against the background of a decrease in the concentration of fibrinogen in the blood and lymph. All this indicates a significant reduction in intravascular coagulation of blood and lymph during such treatment of experimental DM, and the combined use of emoxipin, urokinase and ADLC has an anticoagulant effect. Examination of the rate of lymph flow from the thoracic cavity shows that such treatment also has a lymphastimulatory effect. Lipid metabolism is also affected by changes in the blood and lymph. That is, the amount of HDLP increased against the background of a decrease in the concentration of atherogenic lipids in both blood and lymph. However, there is a difference between the changes that take place in these two liquid environments. For example, while a higher increase in BP compared with baseline (21.7%) was recorded on day 5 of the study, such a

change in lymph (increased by 60.9%) was observed on day 30 of the study (p <0.01). -0.001). As can be seen, the change is more pronounced in the blood than in the lymph. In this regard, there is a difference between the concentration of MDA in the blood and lymph. The amount of RG has also changed in the same direction.

Thus, although RG increased in the blood and lymph compared to the corresponding control group and reached its maximum level on the 60th day, this change was 2.3 times in the blood and 2.1 times in the lymph (p <0.001). That is, although the lipid composition of the blood and the port also underwent changes in the same direction after such treatment, they differed in the degree of change. For example, although HDLP increased in both systems, it was more pronounced in the blood.Such changes can be observed both when comparing the results obtained with the initial and the indicators of the relevant control group. For example, the highest number was recorded on the 60th day of the study (an increase of 2.4 times) compared to the baseline, and in the lymph on the 30th day of the study (an increase of 54.9%). Similar differences can be observed when comparing the results with those of the relevant control group.Thus, although the change reached its peak in the blood and lymph on the 60th day of the study compared to the control group, this increase was 5.3 times in the blood and 4.6 times in the lymph (p <0.001).

Emoxipin and urokinase were also injected in combination with ADLC during unilateral occlusion of the femoral artery in the background of experimental DM. Studies have shown that the parameters studied in the blood and lymph are subject to profound changes. Intravascular coagulation of blood and lymph is more persistently weakened, lymphatic drainage of tissues is intensified. At this time, the changes in LM and LPO deepened, and such treatment had a stronger antioxidant and lymphastimulant effect.

RESULTS

1. A comparative analysis of the results of clinical and experimental studies showed that circulatory disorders in the lower extremities during DM are accompanied by changes in

the vascular wall, disruption of intravenous mechanisms not only in the vascular system but also in the lymphatic system[1;2].

2. Increased atherogenic lipids in the lymph along with blood, activation of LPO, the appearance of markers of endothelial dysfunction increased intravascular coagulation, and most importantly, weakening of the LFR from the onset of breast flow (55) in the background of chronic hyperglycemia in experimental DM. Decreased to 6% indicates the creation of favorable conditions for the disruption of not only microhemocirculation, but also microlimascirculation (p< 0.001) [7;9].
3. Modeling of unilateral occlusion of the femoral artery against the background of experimental DM, in addition to leading to further deepening of the disorders found in the blood and lymph, also significantly weakened the process of lymph formation and transport. In this case, there are favorable conditions for the formation of thrombi in the microvasculature, the accumulation of toxic metabolic products in the intercellular space, the development of intoxication and edema, and this danger is observed until the end of the study [2;12].
4. A comparative analysis of the results obtained during the study of blood and lymph revealed that modeling of experimental DM and unilateral occlusion of the femoral artery against this background, ie violation of the main arterial blood flow, not only to disrupt microhemocirculation, ie to disrupt the transport of nutrients and oxygen to tissues causes edema and purulent-necrotic processes and, consequently, favorable conditions for the development of DPS [4;10].
5. The administration of antioxidant Emoxipin to experimental DM-modeled rabbits not only weakened LPO (the antioxidant effect of Mexicor was accompanied not only by a decrease in LPO production but also by an increase in QSH), as well as a decrease in atherogenic lipid concentration in the blood and lymph. and, most importantly, significantly improved microcirculation. The latter has been shown in our studies to be

2.4 times higher in LAS than in breast milk, especially in control animals (p & lt; 0.001) [5;10].

6. Injecting fibrinolytic-urokinase into experimental DM-modeled rabbits not only increased the fibrinolytic activity of blood and lymph, but also had a significant anticoagulant and antioxidant effect, significantly reduced the amount of atherogenic lipids in the blood and lymph. The fibrinolytic and lymphastimulatory effects of urokinase have become more pronounced. Thus, LFR was 2.6 times higher than the breast flow, especially compared to the control group (p & lt; 0.001) [8;11].
7. A more rational therapeutic effect was observed with the combined use of emoxipin, urokinase and ADLC which can affect various mechanisms of pathogenesis of DPS. Thus, the combined use of emoxipin, urokinase and ADLC in the simulated unilateral occlusion of both the experimental DM and the femoral artery in this background not only prevented the activation of LPO, reduced the concentration of atherogenic lipids in the blood and lymph, continuously eliminated intravascular coagulation (within 60 days). markers of coagulation activation (VF, FDP were not seen), and most importantly, led to a significant increase in LFR from the breast. The latter suggests that such treatment eliminates the pathogenetic mechanisms that are crucial in the pathogenesis of DPS by improving not only microchemocirculation but also microcirculation [6;12;13].

PRACTİCAL RECOMMENDATİONS

1. In diabetes, along with microhemocirculation, microcirculatory circulation is also impaired. The latter, disruption of the transport of toxic metabolic products from the intercellular space, the development of intoxication, edema and, consequently, purulent-necrotic complications create favorable conditions for the development of AED. All this requires taking into account the changes in the lymphatic phase of

microcirculation when designing a scheme of treatment and prevention of purulent-necrotic complications.

2. It is more appropriate to use emoxipin and urokinase in combination with ADLC to achieve a more rational therapeutic effect in the treatment and prevention of DPS. Thus, such a treatment regimen ensures the continuous improvement of not only microhemocirculation, but also microcirculation by eliminating the pathogenetic mechanisms that are crucial in the development of DPS.

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LİST OF ABBREVİATİONS AND SYMBOLS

ADLC – antidiabetic lymphatic collection
AFO – active forms of oxygen
AT-III – antitrombin-III
CA – catalase activity
CDLE – circulatory disorders of the lower extremities
CİM – complex intima media
CRCF – clotting-reverse clotting-fibrinolysis
DAR – diabetic angioretinopathy
DC – dien conjugates
DM – diabetes mellitus
DPAT – duration of partially activated thromboplastin
DPS – diabetic paw syndrome
FDM – fibrin degradation products
FA – fibrinolytic activity
FD – fibrin duration
FFA – free fatty acid
FR – free radicals
FRP – the process of free radicalization
HDLP – high-density lipoproteins
IDDM – insulin-dependent diabetes mellitus
INR – International normalized ratio
KT – kaolin term
LDLP – low density lipoproteins
LFR – lymph flow rate
LM – lipid metabolism
LPO – lipoperoxidation
NİDDM – non-insulin dependent diabetes mellitus
OS – oxidative stress
PD – prothrombin duration
RG – restored glutathione
RQT – restored glutathione
SCFM – a soluble complex of fibrin monomers
SHAİ – shoulder-ankle index
TD – thrombin duration

USDG – ultrasound dopplerography
VLDLP – very low density lipoproteins
VF – Villebrand factor
WHO – World Health Organization

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