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ABSTRACT

of the dissertation for the degree of Philosophy

CORRECTION OF DISORDERS OF BONE METABOLISM AND TISSUE LYMPHADRAINAGE IN DIABETES

Specialty: 3243.01- Pathological physiology

Field of science: Medicine

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Baku-2025

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GENERAL CHARACTERISTICS OF THE WORK

Relevance of the topic and degree of development. Diabetes mellitus (DM) continues to be a serious medical and social problem for the health care system worldwide. In modern times, the rapid spread of DM, the increase in disability and death due to this disease is observed. Diabetes is a disease that affects about 2% of the world's population. According to 2021 data from the World Health Organization (WHO), 537 million people worldwide suffer from diabetes, which means one in ten people. In 2021, the number of deaths from DM was 6.7 million. If this trend continues, the number of patients suffering from diabetes is expected to reach 643 million by 2030, and 783 million by 2045[1]. Type I and II DM is a broad-spectrum chronic metabolic disease characterized by hyperglycemia that causes multisystem effects, and is observed with acute and chronic complications. As a rule, damage to micro and macro vessels is observed in the development of complications of DM. It is noted that the development of vascular complications in both type 1 and type 2 diabetes is caused by a violation of the ratio of insulin and glucose. At this time, the glucose already formed against the background of insulinopenia is combined with proteins without the participation of enzymes and glycoproteins (EPG) are formed. As we know, there is a relationship between the non-enzymatic glycosylation process and the development of vascular endothelial dysfunction. The resulting EPG are persistent compounds, they settle on the vessel wall, cause damage to the endothelium and intima membrane of micro and macro vessels, increase bone resorption, release and activate procoagulants, and cause changes in the hemostasis system. At this time, the supply of tissues and organs with oxygen and nutrients is disrupted, oxidative stress develops. Thus, various manifestations of diabetic angiopathy include stroke, myocardial infarction, retinopathy, nephropathy, macroangiopathy of the lower extremities, neuropathy, etc. such complications develop. As we mentioned, the resulting diabetic

[1] International Diabetes Federation. IDF Diabetes Atlas, 9th edn. Brussels, Belgium: International Diabetes Federation; 2019, p.176

angiopathy has a negative effect on all organs, including bones[2]. In the medical literature, there is a correlation between the degree of severity of DM and the loss of bone mass. A decrease in mineral density in bone tissue is observed in a large percentage of DM patients[3]. As we know, bone is a dynamic organ that is constantly changing and renewing itself. Normally, there is a balance between bone formation and resorption. According to many researchers, DM causes a decrease in bone mass and its mineral density[4]. As a result, bone regeneration is disrupted. An absolute deficiency of insulin reduces the synthesis of collagen and alkaline phosphatase by osteoblasts, which are necessary for the formation and mineralization of the bone matrix, and weakens the stimulation of osteoblasts. Currently, the loss of bone mineral components and the subsequent damage of bone tissue is considered as a chronic complication of DM. Both type I and type II DM have a negative effect on the bone system, causing a decrease in the quality and strength of the bones, an increase in the risk of bone fractures and a violation of the restoration of the damaged bone matrix, and a decrease in the quality of life of patients, causes disability and death.

All this requires a more in-depth study of the pathogenesis of diabetic osteopathy, which is of great medical and social importance, and the development of adequate methods of prevention and treatment. ccording to most researchers, osteopenia is an early symptom in DM[5,6.]

[2] Гоженко А. И., Эндотелиальная дисфункция в патогенезе осложнений сахарного диабета. Сообщение 1. Эндотелиальная функция: этиология, патогенез и методы диагностики //Эндокринология, Украина, 2017, Т.22, №2, с. 171-181.

[3]. Yongwatana K,Supasyndh O,satirapoj B.J.Renal Effects of Sulodexide in Type 2 Diabetic Patients without Nephrotic Range Proteinuria.Diabetes res.2020 Aug 8,2020,2984680.doi:10.1155/2020/2984680.

[4] Драпкина О.М. Особенности ведения пациентов с остеопорозом и сахарным диабетом, // Общественная система усовершенствования врачей, 17 марта 2014, с.84.

[5] Murray C E,Coleman CM.Impact of diabetes mellitus on bone health.IntJMol Sci 2019,20(19),p.4873

[6] Sheu A., Christopher P. et.all Bone metabolism in diabetes: a clinician's guide to understanding the bone–glucose interplay, Diabetologia 2024, 67, p. 1493–1506 https://doi.org/10.1007/s00125-024-06172-x

Thus, non-collagenous osteocalcin, which is a protein of the bone matrix, forms the basis of bone tissue. At the same time, the lack of insulin creates a deficit of active metabolites of vitamin D, which in turn causes a decrease in the absorption of calcium in the intestine, an increase in the secretion and activity of PTH[7]. Various disturbances in the hemostasis system are also observed in DM. Due to multiple disturbances of all chains of the hemostasis system, atherothrombotic condition is observed in DM. Disturbances in the hemostasis system during DM lead to the development of micro and macro-vascular complications[8]. Activation of metabolic processes during hyperglycemia causes an increase in the amount of free radicals and the formation of oxidative stress. Oxidative stress weakens the activity of β-cells of the islets of Langerhans of the pancreas and accelerates the progression of diabetes[9]. So, despite the positive results obtained in the study and treatment of the pathogenesis of DM, in modern times, only the appointment of insulin and diet therapy cannot fully achieve the weakening of the development and progression of angiopathy. For this reason, the need to study the lymphatic system in the development of DM and its complications[10].

It is known that the lymphatic system plays an important role in the transport and detoxification of toxic products of the disturbed

[7]Shen L,Zhuang Q-S,Ji H-F.Assesment of vitamin D levels in type 1 and type 2 diabetes patients;Results from metaanalysis.Mol Nutr FFood Res.2016,60(5),p.1059-1067.https;//doi.org/10.10Q2/mnfr.201500937 . .

[8] Петрик Г.Г., Павлищук С.А. Показатели метаболизма и гемостаза у больных сахарным диабетом 2-го типа с различной выраженностью ангиопатий // Москва: Проблемы эндокринологии, 2010.56(2), с.15-19.

[9] Domingueti CP, Dusse LMS, Carvalho MDG, et al. Diabetes mellitus: The linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complications. 2016, 30(4), p.738-745.

[10] Conte C,Epstein S,Napoli N.insulin resistance and bone:a biological partnership.Acta Diabetologica 2018,55(4),p.(305-314)

exchange from the intercellular areas during various diseases, including diabetes. Therefore, studying the role of the lymphatic system in the development of diabetic osteopathy is the most important issue.

The object and subject of the research. The object of the study is rabbits in which diabetic osteopathy was created in the experiment. The subject of the study is to study the hemostasis system and oxidative stress markers in both fluid environments of animals in the development of diabetic osteopathy during diabetes modeled in rabbits using alloxan, to obtain information about their correction with drugs and lymphatic drainage of tissues.

Research goals and objectives. The aim of the study is to determine the role of the lymphatic system in bone metabolism disorders by determining bone metabolites, hemostasis system, and oxidative stress markers in blood and lymph during alloxan-induced diabetes in rabbits, and to develop an adequate correction method for the advanced pathological process.

Tasks of the research:

1. To determine markers characterizing bone metabolism, oxidative stress, and hemostasis system indicators, as well as lymph flow velocity, in the blood and lymph of intact rabbits;
2. To create a diabetes model in rabbits using alloxan and to comparatively study bone metabolites, oxidative stress markers, and coagulation cascade indicators in the blood and lymph of the animals, as well as to determine the flow rate of lymph;
3. To study the comparative effects of the separate use of lantus solostar(insulin glargin), angioflux(sulodexid), and vitamin D (calciferol)on metabolic changes in bone, oxidative stress markers, and coagulation indicators in the blood and lymph of animals in the treatment of diabetic osteopathy caused by alloxan-induced diabetes in rabbits, and to determine the flow rate of lymph.
4. To study the comparative effect of the combined use of lantus solostar(insulin glargin), angioflux(sulodexid), and vitamin D (calciferol)on metabolic changes in bone, oxidative stress markers, and coagulation indicators in the blood and lymph of

animals in the treatment of diabetic osteopathy caused by alloxan-induced diabetes in rabbits, and to determine the flow rate of lymph;

Research methods. In order to fulfill the goals and tasks set in the research work, experiments were carried out to study the relationship between the metabolic disorders in the blood and lymph of the DM model rabbits (81 head rabbits), the changes that occur in the bone, the intravascular coagulation system, and the changes that occur during oxidative stress and their role in the development of diabetic osteopathy. was carried out in the direction of All experimental animals were grouped into control and experimental series. First, the indicators of blood and lymph were studied in the rabbits included in the I control group. At the next stage, these examinations were performed on rabbits (II control group) created the DM model. Later, in the DM modeled rabbits included in the experimental groups, firstly the antidiabetic properties of lantus solostar, the anticoagulant property of angioflux, and the wide range of vitamin D separately and complex applied to the studied indicators in the blood and lymph, as well as the lymphatic drainage properties of the tissues. effect has been studied.

PRINCIPAL PROVISIONS EXCLUDED IN DEFENSE

1. Markers characterizing metabolic changes in bone tissue during diabetes modeled in rabbits by alloxan are detected in both humoral environments (blood and lymph) of the animals.
2. Pathological changes in oxidative stress, coagulation, anticoagulation, and fibrinolytic systems that develop during alloxan-induced diabetes in rabbits slow down the evacuation of extracellular fluid.
3. In the pathogenesis of functional insufficiency of tissue lymphatic drainage, a combination of lantus solostar(insulin glargin), angioflux(sulodexid), and vitamin D (calciferol)is used as a pathogenetic treatment in cases of impaired bone metabolism, increased oxidative stress, and imbalance between the coagulation cascade.

Scientific novelty of the research.

1. There is a correlation between diabetic osteopathy and the functional state of the animal's blood and lymph system, oxidative stress, and lymphatic drainage of tissues during alloxan-induced diabetic retinopathy in rabbits.
2. The role of functional insufficiency of lymphatic drainage of tissues in the pathogenesis of diabetic osteopathy and its complications has been determined.
3. For the first time, the combined use of lantus solostar(insulin glargin), angioflux(sulodexid) and vitamin D(calciferol) in alloxan-induced diabetes in rabbits had a positive effect on the indicators studied in both fluid environments of animals and the achievement of a long-term therapeutic effect was proven.

Theoretical and practical significance of research. Scientific results obtained based on studies conducted in blood and lymph during modeled alloxan diabetes are of theoretical and practical importance. It has been established that not only blood circulation, but also disruption of lymphatic circulation, i.e. tissue lymphatic drainage, plays an important role in the occurrence of metabolic changes in bone tissue during DM. During diabetic osteopathy, a change in the level of CAF indicators and oxidative stress indicators is observed. During the research, a violation of the lymphatic drainage function of tissues is determined. At this time, the accumulation of toxic products of the disturbed exchange in the intercellular and perivascular areas creates the conditions for the development of complications during DM. During modeled alloxan diabetes mellitus, the markers of metabolic changes in bone tissue, CAF and oxidative stress indicators, as a result of the separate use of lantus solostar, angioflux and vitamin D, which have different mechanisms of action, were observed to change in the direction of the normal level of indicators in both blood and lymph. . The combined use of drugs with different mechanisms of action mentioned above had a positive effect on the studied indicators in both blood and lymph, and a more positive therapeutic effect was obtained.

Approval and application. Separate fragments of the dissertation were written for dedicated to the 80th anniversary of M. Jafarov in the

scientific-practical conference (Baku-2022), in the scientific-practical journal "Health" (Baku-2022), in the international scientific-practical congress dedicated to the 100th anniversary of the birth of the national leader Heydar Aliyev (Baku-2023), Ежемесячный научно-практический информационно-аналитический журнал (Минск, 2023), as well as in the preliminary inter-departmental discussion (06.12.2024, protocol no.5) and it was reported and discussed at the seminar of the approval council (28.02.2025,protocol no.2) organized under the FD 2.07 Dissertation Council of AMU. The results of the research are used in conducting lectures and practical exercises at the Department of Pathological Physiology of the Azerbaijan Medical University.

Published scientific works. 21 scientific works dedicated to the topic of the dissertation have been published. 11 of them are articles and 10 are theses. 1 of the articles was published in a foreign country (Belarus), 10 were published in the publications recommended by the EAC under the President of the Republic of Azerbaijan also included in the international indexing and summarizing databases. Including 1 article without co-authorship. 4 of theses was published abroad (Turkey Canada), and 6 were published in the materials of international and republican level congresses and conferences.

The structure and scope of the dissertation.The dissertation is written in Azerbaijani language on 210 pages (255671 characters), including introduction (10 pages, 17456 characters), literature review (16 pages, 29238 characters), materials and methods (11 pages, 15380 characters), chapter 3 personal research (22 pages , 25737 signs), chapter 4 (99 pages, 134797), from the conclusion (16 pages, 30090 characters), it consists of conclusions (2 pages, 2289 characters), practical recommendations (1 page, 684 characters) and a list of literature sources (39 pages) and conditional abbreviations. Dissertation work consists of a list of literature, which includes 185 literature sources. Of these sources, 8 local authors, 5 Turkish, 58 Russian, and 114 English authors were cited. The work is illustrated with 31 tables and 35 pictures.

THE MAIN CONTENT OF THE DISSERTATION

In the introductory part of the dissertation, the relevance, purpose, tasks, methodology, scientific novelty and practical importance of the research work were noted, information was given about the main provisions, approval, volume and structure of the defense.

The first chapter of the dissertation is written based on the literature review. The works and scientific considerations of domestic and foreign researchers about the role of the hemostasis system and oxidative stress in the development of diabetes and its complications, especially diabetic osteopathy, were analyzed. Here, the occurrence of diabetic osteopathy as a complication of diabetes and the ways of its elimination are investigated. Based on literature data, indicators of the hemostasis system and oxidative stress, which play a role in the development of diabetic osteopathy, were studied and analyzed. In the second chapter of the dissertation, the stages of the research are shown, and information is given about the materials and methods of the experiment. Experimental studies were conducted on 81 rabbits of both sexes, weighing 2.5-3.0 kg. Experiments on animals were carried out in accordance with the requirements of the European Convention on the Protection of Vertebrate Animals and Directive 86/609/EEC. Anesthetization of the animals in the experiment and euthanasia and exclusion from the experiment were carried out in accordance with the requirements of the "Rules for conducting scientific research using experimental animals" [Council Directive of November 24, 1986]. The blood needed for the study was taken from the heart cavity, and the lymph was taken from the chest lymph flow. Removal of lymph from the breast. A.A. Kornienko and others. [1977] to the method of M.X. It is based on the modified method given by Aliyev and V.G. Mammadov [1990][11,12].

[11] Məmmədov Y.C,Əliyev., O.S Əliyev S.H və b Eksperimental şəkərli diabet zamanı toxumaların limfadrenajının pozulmasında endotelial disfunksiyanın rolu//5th Baku International Medical Congress,Baku,2018,p.146 .

[12] Talışinskaya M.B., İbrahimova G.H və .Şəkərli diabet zamanı qanın və limfanın laxtalanma sisteminin pozulması və onların korreksiyasının bəzi prinsipləri .//Sağlamlıq Elmi praktik jurnal ,Bakı ,2022

The surgical operations performed during the procedure, i.e. opening of the breast lymph duct and draining it, taking of lymph and blood, were performed under anesthesia. For the purpose of anesthesia, 8 mg/kg of calypsol and 0.15 ml/kg of 1% diphenhydramine solution were injected into the ear vein of rabbits. To create a model of diabetes, "Chinchilla" rabbits were starved for 24 hours without interruption of water intake. After 24 hours, a single dose of 5% alloxan monohydrate solution at a dose of 100 mg/kg was intravenously injected into the peritoneal cavity of the animal, and a model of DM disease was created in rabbits[13]. DM model was established in rabbits in experimental and treatment groups. The rabbits we used in the experiment were placed in 6 groups. There were 8 rabbits in the control group, 13 rabbits in the experimental group, and 15 rabbits in each of the treatment groups. Preparatory work was carried out in the rabbits in the control group, and blood and lymph were taken from the animals before modeling the DM disease in order to study the studied indicators. The lymph flow rate was determined based on the amount of lymph collected per kilogram of the animal's body weight with the help of a cannula inserted into the chest lymph flow (ml.min/kg). The level of glucose was determined in the blood and lymph of rabbits on an empty stomach, that is, before feeding and water in the morning. A 1.5-fold increase in the level of glucose in the blood was assessed as the emergence of a DM disease model in animals. Thus, 72 hours after alloxan injection, diabetic symptoms developed. Sugar concentration in the blood and lymph of animals with modeled DM disease was determined during the study with the help of a dynamic control glucometer device (Senso Lite Nova, Budapest-Hungary). Thus, the sugar level in the blood and lymph of 8 rabbits placed in the control group, markers characterizing bone metabolism, coagulation cascade and oxidative stress indicators, lymph flow rate were determined[13].

[13] Erturk Karaagac Diyabetik Ayak Ülseri ve Yara İyileşmesi-Hayvan Modelleri, december, Izmir Katip Celebi UniversityIn book: Kardiyovasküler Araştırmalarda Deney Hayvanı Modelleri, 2020, pp. 305-322

These indicators were taken as a control or initial indicator. Blood and lymph calcium, phosphorus, vitamin D, osteocalcin, and PTH levels were measured before alloxan administration to assess bone metabolism. Coagulation, as well as anti-coagulation, to assess parameters of the coagulation cascade of blood and lymph in animals during the experiment indicators fibrinogen, PT, Pİ, İNR, TM, PTT and AT III level was determined before alloxan injection. The indicated parameters were determined in the semi-automatic coagulometer "Humaklot Duo" (Germany) with the help of reagent kits developed by "Human" (Germany) and "Koagulotest" (Russia). To evaluate the oxidative stress in the blood taken from the heart cavity and the lymph taken from the breast lymph flow for research, MDA level (L. I. Andreevna, 1988) and AOS indicators of catalasas activity (M. A. Koroliuk et ., 1988) are generally accepted biochemical methods. These examinations were carried out with the help of special reagent sets in the "BioScreen MS-2000" biochemical analyzer made in Germany. The parameters studied in the blood and lymph of rabbits were studied in control group animals without treatment measures.

Animals with 15 rabbits in each of the four treatment groups were assigned separate and combined use of lantus solostar, angioflux and vitamin D, respectively. The numerical expression of the indicators obtained during the research was statistically analyzed based on modern recommendations. Statistical studies were carried out using the application of variation analysis methods in the "IBM Statistik SPSS-26" program. The non-parametric U-Mann-Whitney test was used for comparison of variance ranks.

In the third chapter of the dissertation (control group), information is given about the inclusion of 13 rabbits in the control group, which created the DM model during the experiment. During the study, blood and lymph were taken, and the dynamics of changes in the levels of sugar, markers characterizing metabolic disorders in bone, PTH, the level of CAF system and oxidative stress indicators, and LFR were determined by injecting a 5% alloxan monohydrate solution at a dose of 100 mg/kg into the peritoneal cavity of rabbits. was comparatively studied in blood and lymph of modeled animals for 5, 15, 30 and 45 days. A certain regularity is observed between the

dynamics of changes in sugar levels, diabetic osteopathy markers and PTH activity in the blood and lymph of DM modeled animals.Thus, when studying the level of sugar, markers of diabetic osteopathy, activity of PTH in blood and lymph, it is determined that the indicators change in the same direction in both liquid environments. After 15 days of alloxan injection, sugar levels increased compared to baseline in both fluid media. Towards the end of the study, this indicator increased by more than 1.5 times and reached a high level in both systems. During the study, the level of phosphorus in both blood and lymph increased compared to the initial level, increasing by 4.32 times in the blood and more than 3 times in the lymph on the 45th day. As for the Ca+2 concentration, it decreased in blood and lymph on day 5 of the study compared to the initial values, on day 15 of the study it increased by 1.36 times in blood and by 1.27 times in lymph compared to the value on day 5, and on day 45 of the study, the initial value compared to 1.67 times (up to 40.3%, respectively) and 46.2% decrease in lymph was observed. The level of PTH increased by 18% in the blood and 67% in the lymph compared to the initial level on the 5th day of the study, and on the 30th day of the study, this indicator decreased in the blood and increased by 1.55 times in the lymph ($p< 0.001$).).

The level of vitamin D decreased in both liquid environments depending on the increase in the study period. On the 45th day of the study, the level of vitamin D decreased by 2.84 times (up to 64.86%) in the blood, and by 61.33% in the lymph compared to the initial level ($p< 0.001$). The level of osteocalcin in blood and lymph increased 3.52 times in blood and 2.23 times in lymph compared to the initial level on the 30th day of the study ($p<0.001$).

Thus, a comparative study of the changes in sugar level, diabetic osteopathy markers, and PTH activity in blood and lymph during SHD created in rabbits in an experiment determines that there is a mutual relationship between diabetic osteopathy and lymph drainage functions of tissues.

As the research period increases, the difference of the studied indicators from the initial indicator is more clearly noticeable and

agrees with the literature data[14] The level of CAF system indicators in the blood of DM modeled animals was determined for 5, 15, 30 and 45 days. A certain regularity was observed between the dynamics of the coagulation cascade indicators in the blood and lymph of animals modeled with DM, as well as the flow rate of the taken lymph.

Thus, when studying the indicators of the CAF system in blood and lymph, it was determined that the indicators change in the direction of hypercoagulation in both fluid environments. That is, the level of fibrinogen increased to 73.8% in blood and 66% in lymph on the 45th day of the study compared to the initial level.

During the study period, the level of PT decreased in both liquid environments, at the end of the study, on the 45th day, this indicator decreased to 26% in blood and 58.3% in lymph compared to the initial indicator. On the 5th day of the study, compared to the corresponding indicators of the control group, the level of thrombin time decreased in blood and lymph, on the 45th day of the study, the indicator was determined to decrease by 66% compared to the initial indicator in both fluid environments.

Contrary to the increase in the study period, PTT and INR levels decreased in blood and lymph. On the 45th day of the study, PTT in blood decreased to 61.6%, INR to 59.3%, and PTT in lymph to 59.9% and INR to 78.94%, respectively, compared to the initial indicator in both environments. . The direction of change of the prothrombin index level increased in blood and lymph depending on the increase of the research period. On the 45th day of the study, it was clearly shown that the level of the prothrombin index in the lymph increased more than in the blood. During the study, the level of AT-III decreased in both fluid media, and on the 45th day of the study, it was observed to decrease by 58.3% in the blood and 62.2% in the lymph, respectively,

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[14] Ивченко Л.Г. Разработка и обоснование алгоритма оценки метаболизма костной системы у детей с сахарным диабетом первого типа / Л.Г.Ивченко, И.М.Быков, А.А.Басов, Ф.Н.Гильмиярова [и др.] // Кубанский научный медицинский вестник. 2018, Т. 25, № 5, с. 35-47.

compared to the initial indicator. Changes in the prothrombotic direction are more clearly observed on the 30th day of the study compared to the corresponding indicators of the control group. The dynamics of changes in CAF indicators studied in the blood and lymph of animals modeled with DM deepened as the duration of the study increased.

Based on the information we have learned, we can say that there is a relationship between the level of fibrinogen and insulin[15]. Hyper-fibrinogenemia causes damage to vascular wall endothelial cells and subsequent development of atherothrombotic processes. An increase in the level of fibrinogen is accompanied by an increase in the level of non-enzymatic glycosylation and the degree of angiopathy. Acceleration of PTT and hyperfibrinogenemia are considered as hemostasis markers during DM. Acceleration of prothrombin and thrombin time, decrease of INR determines the occurrence of prothrombotic condition. Activation of the coagulation system is accompanied by a decrease in the activity of the anticoagulation system. Thus, during DM, the increase in the level of EPG was observed with a decrease in AT III activity[16]. During the study, the risk of developing a prothrombotic condition was determined in the blood and lymph of rabbits modeled with DM. As mentioned, a relationship between the dynamics of changes in the blood and lymph of the indicators studied in animals and the dynamics of changes in the lymph drainage function of tissues was observed. During the initial and increasing period of the study, the activation of the coagulation cascade indicators in the blood and lymph in the direction of hypercoagulation, the weakening of the lymph flow rate during the decrease of the activity of the anti-coagulation system indicator is evaluated as the result of the violation of the lymphatic drainage

[15] Wieczór R, Wieczór AM, Kulwas A, Rość D. Type 2 Diabetes and Cardiovascular Factors Contrasted with Fibrinolysis Disorders in the Blood of Patients with Peripheral Arterial Disease. Medicina (B Aires). 2019, 55(7), p.395.

[16] Lemkes BA, Hermanides J, Devries JH, et al. Hyperglycemia: a prothrombotic factor. J Thromb Haemost. 2010,8(8), p.1663-1669

property of the tissues. Taking these into account, it can be noted that the lymphatic drainage function of tissues weakens during the activation of coagulation in blood and lymph in the DM created in the experiment.Both environments are the result of activation of metabolic processes, cell membrane damage and excessive generation of free radicals

At this time, the transportation and cleaning of exchange products collected in the intercellular area is weakened. This also creates favorable conditions for cell and tissue damage during DM. A certain regularity was observed between the dynamics of changes in the level of MDA and the activity of cataLFRe in the blood and lymph of animals modeled with DM. During the progress of the study, the changes in the indicators of oxidative stress and antioxidant system in during DM. On the 5th day of the study, the level of MDA in both blood and lymph increased compared to the corresponding indicators of the control group, and on the 45th day, it increased more than 2 times in both blood and lymph and reached the maximum level . During the research period, cataLFRe activity decreased in both liquid environments. On the 45th day of the study, cataLFRe activity decreased by 44%, compared to the corresponding indicators of the control group. The dynamics of changes in the level of MDA and the activity of cataLFRe studied in the blood and lymph of animals modeled with DM deepens as the duration of the study increases. Thus, an increase in the level of free radicals leads to the formation of oxidative stress. Metabolites generated during hyperglycemia and oxidative stress in DM damage β cells of the pancreas and reduce insulin synthesis and secretion. This accelerates the progressive development of DM. The main reason for the development of oxidative stress is the weakening of the antioxidant defense. During the study period, the level of MDA in the blood and lymph increased during the modeled DM, while the level of LFRe decreased and agreed with the literature data[17].

[17] Алиев М. Х., Алиев С.Д. и др. Оксидативный стресс в патогенезе нарушений микроциркуляции при сахарном диабете // Вестник хирургии Казахыстана, 2017, №1 (50), с.13-17.

Lymph flow rate decreased in rabbits during modeled alloxan diabetes.

On the first 5th day of the study, LFR decreased by 1.02 times, on the 15th day of the study by 1.2 times, on the 30th day by 1.5 times, and on the 45th day by 1.95 times. The weakening of LFR was more clearly observed at the end of the study.

As a result of the conducted research, it was determined that there is a connection between blood and lymph coagulation disorders and bone metabolism during diabetes created in the experiment[18]. Against the background of hyperglycemia, changes in metabolic processes in blood and lymph in bone tissue, increased coagulation, weakening of the lymph flow rate (LFR) cause disruption of the microhemo and microlymphatic circulation system. Thus, during the modeled diabetes, the changes of the markers characterizing the bone metabolism, coagulation cascade and oxidative stress indicators in both blood and lymph as the duration of the study is prolonged have a negative effect on the lymphatic drainage of the tissues against the background of osteopathy, prothrombotic condition and the increase of free radicals. Such a situation is more clearly noticeable in the advanced periods of research. This led to the accumulation of toxic products in the intercellular area, violation of tissue clearance and the creation of conditions for the development of destructive changes[19]. In accordance with the periods of the study, the decrease in the flow rate of lymph from the breast lymph flow was determined. The changes that occurred during the study were accompanied by the decrease of the flow rate of the lymph from the breast lymph flow on the 45th day

[18] Denos.M.et.al.Vitamin D status and risk type of type 2 diabetes in the Norwegian Hunt cohort study:Does family history or genetic disposition modify the association BMJ OPEN Diabetes Res.Care 9 (1)e 0011948.,2021...

[19] Коненков В.И., Климонтов В.В., Кузнецова И.В. Нарушение ангиогенеза и лимфангиогенеза при сахарном диабете // Москва: Архив патологии, 2014, № 2, с. 55

of the study to 48.86% in comparison with the corresponding indicators of the control group.

The fourth chapter of the dissertation (experimental group). In the first subgroup.

During the research, the animals that created the DM model were divided into 4 groups with 15 rabbits in each treatment group. At this stage, the selection of drugs we use for the treatment of modeled animals is aimed at regulating the level of sugar and the indicators we study in the blood and lymph. In the first subgroup, the drug lantus solostar was used for the treatment of modeled animals. Insulin glargine, the active ingredient in Lantus solostar, is designed as an analogue of human insulin. Since this drug injected under the skin is gradually absorbed, it has a long-LFR effect. Therefore, after the effect of the drug, the level of the studied indicators in the blood and lymph of the DM modeled rabbits gradually changes, it is clearly noticeable compared to the initial indicator. The dose of lantus solostar, which we use during the treatment of animals with DM, is corrected based on the level of indicators determined in blood and lymph. After subcutaneous injection of 0.1-0.2 ml/kg of lantus solostar to rabbits modeled with DM, a relative improvement of the level of the studied indicators in both blood and lymph was determined. Thus, the effect of the use of lantus solostar in the treatment of animals with diabetes on the level of sugar in the blood and lymph, on the markers characterizing the metabolism in the bone and on the activity of PTH was determined for 5, 15, 30 and 45 days, and the level of these indicators in both liquid environments change in the same direction was determined. After the subcutaneous injection of lantus solostar for the purpose of treatment, on the 5th day of the study, the sugar level was reduced in both fluids compared to the corresponding indicators of DM modeled animals ($p< 0.001$). During the study, the level of phosphorus in the blood and lymph decreased to 24.1% in the blood and 31.35% in the lymph compared to the corresponding indicators of DM modeled animals on the 45th day of the study ($p< 0.001$). During the study, it was determined that the concentration of Ca^{+2} in the blood was much higher than in the lymph. A decrease in the level of PTH during the study period compared to the indicators of DM

modeled rabbits was determined in both fluid systems. The level of vitamin D increased in both liquid media depending on the duration of the study. The level of osteocalcin in the blood and lymph was determined to increase by 21.5% in the blood and 27.9% in the lymph on the 15th day of the study, and to decrease on the 45th day in both systems, compared to the corresponding indicators of the DM modeled animals. During the treatment of DM modeled animals with lantus solostar, during the progressing period of the study, changes in the indicators of the CAF system in the direction of hypocoagulation were determined. The decrease in the level of fibrinogen was determined on the 5th day of subcutaneous injection of lantus solostar in DM modeled animals and was clearly noticeable on the 45th day of the study period. On the 45th day of the study, a decrease in the level of fibrinogen in blood by 1.07 times (up to 3.4%, respectively) and in lymph by 1.05 times (up to 94.6%, respectively) compared to the indicators on the 15th day of the study has been determined. During the research period, an increase in the level of PT in both blood and lymph was noticed. Regarding the level of thrombin time, after subcutaneous injection of lantus solostar, an increase is determined starting from the 5th day of the study in both systems. On the 3rd day of the study, the level of thrombin time increased by 1.19 times (up to 19.1%, respectively) and in lymph by 1.21 times (up to 21%, respectively) compared to the indicators of the 15th day of the study. PTT and INR levels were observed to increase in blood and lymph according to the increase in the study period. As for the prothrombin index during the study, the direction of change of its level decreased depending on the increase of the study period. On the 45th day of the study, a 1.15-fold decrease in the prothrombin index in the blood and 1.13-fold in the lymph was determined in comparison with the indicators of the 15th day of the study in both systems. Significant changes in the indicators of the antithrombotic system were also determined in the blood and lymph of rabbits injected with Lantus solostar subcutaneously. The increase in AT-III levels throughout the study continued until the end of the study. When examining the level of oxidative stress indicators in the blood and lymph of animals during the subcutaneous injection of lantus solostar for the treatment of

rabbits with diabetes, it was determined that the indicators changed in the same direction in both systems. On the 45th day of the study, the level of MDA in the blood was 1.09 times (up to 8.4%, respectively) and 1.13 times in the lymph (up to 11.9%, respectively) in both systems compared to the values on the 15th day of the study. decrease was observed. On the 45th day of the study, the level of cataLFRe increased by 1.18 times (up to 18%, respectively) in blood and 1.15 times (up to 15%, respectively) in the lymph in both fluid systems compared to the values on the 15th day of the study. has been done. During the subcutaneous injection of lantus solostar for the treatment of diabetic rabbits, on the 5th and 30th days of the study, compared to the initial value of LFR, 1.9 (up to 47.8%, respectively) and 1.38 times (respectively up to 27.7 %), a 1.87-fold decrease (up to 46.8 %) compared to the corresponding indicators of DM modeled animals, and An increase of 1.08 times (up to 8.9%, respectively) was determined. On the 45th day of the study, LFR increased by 1.42 and 1.15 times compared to the indicators of the 5th and 15th day of subcutaneous injection of lantus solostar ($p< 0.001$). The treatment of rabbits with CD with lantus solostar relatively improved the lymphatic drainage function of tissues. Thus, during the subcutaneous injection of lantus solostar for the treatment of rabbits with modeled DM in the experiment, not only the markers characterizing bone metabolism, coagulation cascade and oxidative stress indicators in the animal's blood and lymph improved, but also the relevant indicators of the flow rate of lymph from the breast lymph flow in the previous series of the study. a relative increase compared to Thus, the changes in the level of the above studied indicators in the pathogenesis of complications during diabetes, especially diabetic osteopathy, are consistent with literature data[20]. **In the second subgroup**. During the experiment, angioflux was used in the next stage of the study in order to obtain a relatively stable level of CAF system indicators in the blood and

[20] Johns E.C.,Denison FC.,Norman JE.,Reynolds RM.Gestational Diabetes Mellitus:Mechanisms,Treatment and Complications.Trends Endocrinol Metab.2018,29(11),p.743-754.https://doi.org/10.1016/j.tem.2018.09.004.

lymph, and to stabilize the level of other studied indicators in the treatment of DM modeled in 15 rabbits.

During the study, after 1 ml of angioflux, which we used in the treatment of DM modeled rabbits, was injected into the muscle, changes in blood and lymph system indicators, as well as sugar, markers of diabetic osteopathy, and PTH activity were observed according to the study period. The effect of angioflux on the level of sugar in both liquid media, markers characterizing the metabolism in bone and the activity of parathyroid hormone in the treatment of DM modeled animals was determined for 5, 15, 30 and 45 days. After therapeutic intramuscular injection of angioflux, the sugar level decreased in accordance with the increase in the duration of the study in both liquid media. During the study, the level of phosphorus in the blood and lymph decreases compared to the corresponding indicators in the previous series of the study. On the 45th day of the study, the level of phosphorus in the blood decreased from 152.5% to 41.6% and to 23.1% compared to the corresponding indicators of the initial, DM modeled animals and III series, and 103.7% in the lymph. - to 41.7% and its decrease to 15% was determined. On the 45th day of the study, the decrease in the concentration of Ca+2 in the blood from 44.8% to 142.6% and to 29.48% compared to the corresponding indicators of the initial, DM modeled animals and III series, in lymph 4, Its increase from 3% to 78.1% and up to 1.7% was determined. A decrease in the level of PTH compared to the corresponding indicators of the previous series on 5 days of the study was determined in both liquid media. The level of vitamin D increased in both liquid media depending on the duration of the study. On the 45th day of the study, the level of vitamin D in the blood increased from 35.9% to 82.4% and up to 13.4%, compared to the corresponding indicators of the initial, DM modeled animals and III series, and in the lymph - 33.8% from to 71.17% and its increase to 17.76% was determined. The level of osteocalcin in blood and lymph decreased in both fluid environments depending on the increase in the study period. After intramuscular injection of Angioflux, on the 45th day of the study, the level of osteocalcin in the blood decreased from 130,2% to 38,7% and to 16,92% compared to the corresponding indicators of the initial, DM modeled animals and

series III, and in the lymph 50 Its decrease from % to 39,1% and to 16,86% was determined. Thus, a comparative study of changes in blood and lymph of sugar level, markers of diabetic osteopathy, and PTH activity during the treatment of diabetic osteopathy with angioflux in rabbits indicates that there is a mutual relationship between diabetic osteopathy and lymphatic drainage functions of tissues. As the research period increases, it becomes more noticeable that the studied indicators differ from the corresponding indicators of the control group and DM modeled animals. In the treatment of DM modeled animals with angioflux, changes in the level of CAF system indicators in both fluid environments in the direction of hypocoagulation were determined. Thus, the drug angioflux has antithrombotic, hypolipidemic, angioprotective, fibrinolytic and direct anticoagulant effects, inhibits the activated factor X of coagulation and reduces the concentration of fibrinogen in pLFRma. The use of the drug causes changes in the direction of hypocoagulation to be more clearly observed in both liquid environments starting from the 5th day of the study. The dynamics of the results obtained during the study were also determined when comparing them with the corresponding indicators in the previous series of the study. The angioprotective property of Angioflux is based on the restoration of the structural and functional integrity of the vascular endothelium[21]. During the study, the level of fibrinogen in the blood and lymph decreased compared to the corresponding indicators in the previous series of the study. After intramuscular injection of Angioflux, on the 45th day of the study, the level of fibrinogen in the blood increased from 32.5% to 23.8% and to 13.5%, compared to the corresponding indicators of the initial, DM modeled animals and III series. decrease, from 30.4% to 21.6% and 14.83% decrease in lymph was determined. On the 5th day of the study, it was determined that the level of PT in both fluid environments of the animal was prolonged compared to the corresponding indicators of the initial, DM modeled animals and the III series.

[21] Sapkota B.,Shrestha S.K.,Poudel S.Association of activated partial thrombopLFRtin time and fibrinogen level in patients with type 2 diabetes mellitus.BMC RES Notes.2013,6(1),p.485.

After intramuscular administration of Angioflux, thrombin time levels decreased from 19.75% and 29.8% to 129% and 101.8% compared to baseline, DM modeled animals and series III in both fluid media on day 45 of the study. up to 18.8% and 15.6%. During intramuscular injection of Angioflux, PTT and INR levels were observed to increase more in the lymph than in the blood, according to the increase of the study period. As for the prothrombin index during the study, the direction of change of its level decreased more in the blood than in the lymph, depending on the increase of the study period. Significant changes in the indicators of the antithrombotic system were also determined in the blood and lymph of rabbits injected with 1 ml of Angioflux intramuscularly. At study day 45 after intramuscular administration of angioflux, AT-III levels in both fluid media increased from 19.9% and 26.9% to 90.8% and 93.6% compared with baseline, DM modeled animals, and III-series respectively. and its increase to 5.4% and 9.4% was determined. After intramuscular administration of Angioflux, MDA levels in both fluid media increased from 60% and 42% to 41.6% and 41.98% compared to baseline, DM modeled animals and series III, respectively, on day 45 of the study, and 22, Its decrease to 9% and 21.3% was determined. Regarding the level of cataLFRe, after intramuscular injection of 1 ml of angioflux, on the 45th day of the study, the level of cataLFRe was determined to increase by almost the same percentage (from 13.9% to 52%) compared to the corresponding indicators of the initial, DM modeled animals and series III in both fluid media. ,4% and up to 23%). 1.36 (up to 26.8%) and 1.26 times the LFR on the first 5th and 30th day of the study during the treatment of rabbits with DM by 1.36 times (up to 26.8%) and 1.26 times (respectively up to 20.84 %) decrease, 1.34 times (respectively 25.52 to %)) and 1.19 times (to 19.1%, respectively) increase was determined. On the 45th day of intramuscular injection of Angioflux, the level of LFR increased by 1.1 times compared to the indicator on the 15th day of the study.

On the 45th day of the study, the level of LFR increased by 1.15 times compared to the corresponding indicators of the III series ($p< 0.001$). A relative increase in the level of LFR compared to the

corresponding indicator in the previous series of the study was determined.

Angioflux treatment of CD rabbits significantly improved tissue lymphatic drainage function. During the injection of 1 ml of angioflux into the muscle for the treatment of rabbits with DM, it had a certain effect not only on the indicators of the CAF system in the blood and lymph of the animal, but also on the markers characterizing the metabolism in the bone and indicators of oxidative stress.

At this time, it was determined that the LFR obtained from the breast lymph flow was relatively increased compared to the corresponding indicators in the previous series of the study.

However, the difference in the level of the obtained indicators compared to the corresponding indicators in the previous series of the study was determined. As we know, chronic hyperglycemia in DM also creates conditions for the development of oxidative stress. The free radicals generated at this time damage the endothelium of the vascular wall, create conditions for the emergence of a prothrombotic state and the development of vascular complications.

This further causes cell damage to continue and the accumulation of toxic waste products in the tissues to linger there.

In general, when analyzing the results of our research work, we can say that although the treatment of modeled DM with angioflux during the experiment affects the indicators we studied in both liquid environments of the animal, although the lymphatic drainage of the tissues is satisfactory, the level of the indicators we get is different from the level of normal indicators. has done

In the third subgroup. It was determined that diabetic osteopathy markers, sugar level, and parathyroid hormone activity were altered in the treatment of DM modeled animals with vitamin D in both blood and lymph.

Based on the literature data written above, vitamin D deficiency can be considered a risk factor in the development of type I diabetes[22].

[22] Keleştimur H. Paratiroit hormonu ve kalsiyum-fosfat metabolizması. İçinde Ağar E, İnsan fizyolojisi.1. Basım. İstanbul Tıp Kitapevleri; 2021, p. 966-967

Lack of insulin, which plays a role in the pathogenesis of type I DM, causes a decrease in the activity of enzymes involved in vitamin D metabolism (Ikeda). In type I DM, vitamin D plays a role in the regulation of the functioning of β-cells of the pancreas and glycemic control.Therefore, the appointment of vitamin D to patients with DM shows a positive result[23]. Vitamin D has an anti-inflammatory effect, reduces the occurrence of diabetes and the frequency of its complications. As we know, vitamin D plays a role in calcium-phosphorus metabolism and ensuring bone mineral density. Recently, vitamin D has been studied as a steroid hormone that provides many physiological processes in the human body[24]. Vitamin D increases the level of intracellular calcium and causes the secretion of insulin by beta cells, as a result of which the blood sugar content is regulated. A compensatory increase in PTH secretion during insulin deficiency and hypocalcemia is considered to be the main factor in the pathogenesis of diabetic osteopenia. So, since the lack of vitamin D is considered as an independent risk factor for the development of metabolic disorders, including diabetes, we considered it appropriate to give vitamin D to animals in our research work[25].

Based on the above, sugar level, diabetic osteopathy and vitamin D was used in the next phase of the study to bring oxidative stress markers, CAF system indicators to normal levels in blood and lymph.

On the 5th day of daily administration of vitamin D to animals for the purpose of treatment, it was observed that the sugar level in both liquids decreased compared to the corresponding indicators in the previous series of the study. On the 45th day of the study after the daily

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[23] Kanazawa I,Sugimoto T.Diabetes mellitus-induces bone ftagility.Intern Med 2018,7(19),p.2773-2785.

[24] Ordooei M, Shojaoddiny-Ardekani A, Hoseinipoor SH, et al. Effect of vitamin D on HbA1c levels of children and adolescents with diabetes mellitus type 1. Minerva Pediatr. 2017, 69(5), p. 391-395.

[25] Поваляева А.А., Пигарова Е.А., Дзеранова Л.К., Рожинская Л.Я. Взаимосвязь статуса витамина D с развитием и течением сахарного диабета 1 типа. Ожирение и метаболизм. 2020,17(1), с. 82 -87.

administration of vitamin D, the initial indicator of the level of phosphorus in the blood was from 73.9% to 59.74% and 46.99% compared to the corresponding indicators of DM modeled animals, III and IV series. from to 31.1%, and in lymph from 58.4% to 54.6% and from 33.9% decreased to 22.3%.

On the 30th day of the study, the concentration of Ca+2 in the blood increased from 11.3% to 63.8% and from 42.7% to 25.3% compared to the corresponding indicators of the initial DM modeled animals, III and IV series. The decrease to % was determined. It was determined that the level of PTH decreased in both liquid environments according to the increase of the study period. The level of PTH decreased from 14.6% to 8.8% compared to the corresponding indicators of series III and IV in the blood on day 45 of the study, and in the lymph compared to the baseline, DM modeled animals, the corresponding indicators of the series III and IV compared to 5.6% to 32.5% and from 9.3% to 3.6%.. The level of vitamin D increased in both liquid media depending on the duration of the study. On the 45th day of the study, the baseline level of osteocalcin in the blood decreased from 100% to 46.7% and from 27.9% to 13.2% compared to the corresponding values of DM modeled animals, series III and IV, and in the lymph it decreased from 27.02% to 48.4% and from 29.6% to 15.4% is defined. During the treatment of DM modeled animals with vitamin D, changes in the level of CAF system indicators in the direction of hypocoagulation were determined in both liquid environments. On the 45th day of the study, it was determined that the level of fibrinogen in the blood decreased from 25.94% to 14.5%, from 26.7% to 13.9% in the lymph compared to the corresponding indicators of the III and IV series. On the 45th day of the study, it was determined that the level of PT in both fluid environments of the animal increased compared to the corresponding indicators of the previous series. That is, an increase in the level of PT in the blood from 49.4% to 10.4%, and from 33.6% to 9.4% in lymph compared to the corresponding indicators of the III and IV series was determined. The level of thrombin time on the 45th day of the study in both fluid media, the initial indicator in the blood compared to the corresponding indicators of DM modeled animals, III and IV series, from 7.7% to

163.6%, from 36.7% to 15 %, from 12.7% to 150.9% in lymph, from 43.7% to 24.3% has been determined. PTT and INR levels were observed to increase in blood relative to lymph according to the increase in the study period. As for the prothrombin index during the study, the direction of change of its level decreased depending on the increase of the study period in both liquid environments. On the 30th day of the study, the level of the prothrombin index in both fluid environments of the animal was from 25.7% to 5.4% in the blood, from 29.4% to 6.7% in the lymph compared to the corresponding indicators of the III and IV series. decrease has been determined. After the effect of vitamin D, significant changes in the indicators of the antithrombotic system were determined in the blood and lymph of rabbits. On the 45th day of the study, an increase in the level of AT-III from 17.3% to 11.3%, from 17.01% to 6.9%, compared to the corresponding indicators of the III and IV series was determined in both liquid media. . In the treatment of DM modeled animals with vitamin D, changes in the level of oxidative stress indicators are detected in both fluid environments. On day 45 of the study, MDA levels in both fluid media ranged from 22.6% to 55.5%, 12.8% to 23.8% in blood compared to the corresponding values of baseline, DM modeled animals, series III and IV to , a decrease in lymph from 11.1% to 54.8%, from 38.6% to 21.99% has been determined. As for the level of cataLFRe, on the 45th day of the study, it was determined that the level of cataLFRe increased by almost the same percentage (from 8.91%) compared to the corresponding indicators of the beginning, DM modeled animals, III and IV series in both liquid environments. up to 61.2%, from 30% to 5.7%). During the daily use of vitamin D for the treatment of diabetic rabbits, on the first 5th and 30th day of the study, compared to the initial value of LFR, 1.11 times (up to 10.5%, respectively) and 1.06 times (respectively up to 6.6 %), a decrease of 1.09 times (up to 8.9 %) and 1.4 times (up to up to 40.7 %) was determined. On the 45th day of the study, the level of LFR increased by 1.05 times compared to the indicator on the 15th day of the study. On the 45th day of the study, the level of LFR increased by 1.26 times (up to 26.3%, respectively) and 1.08 times (up to 8.9%,

respectively) compared to the corresponding indicators of the III and IV series ($p < 0.001$).

It was observed that the level of LFR increased compared to the corresponding indicators in the previous series of the study. During the use of 2-10 drops of vitamin D per day for the treatment of rabbits with DM, not only the stabilization of the levels of the markers characterizing the bone metabolism, LEP system and oxidative stress indicators in the blood and lymph of the animal, but also the LFR obtained from the breast lymph flow was also observed in the study. an increase compared to the corresponding indicators in the previous series was determined.

During the administration of vitamin D to rabbits modeled with DM, the decrease in the level of sugar in the blood and lymph caused the weakening of non-enzymatic glycosylation, the relative restoration of the completeness of the vascular endothelium, and the development of processes in the direction of hypocoagulation. Thus, it can be concluded that a positive clinical effect was obtained during the administration of vitamin D in the treatment of rabbits modeled with diabetes, the stabilization of glycemic control and the weakening of the progressive development of complications were determined against the background of the restoration of undamaged beta cells[26,27.]

The fourth subgroup. The next preparations used in the treatment of DM modeled rabbits consisted of the joint administration of lantus solostar, angioflux and vitamin D (cholecalciferol). The determination of the level of the studied indicators in both liquid environments is consistent with the literature data that we examined about the occurrence of diabetic osteopathy[28,29]. In the experiment, the drugs we used separately in the treatment of rabbits modeled with DM enabled the stabilization of the sugar level, markers of diabetic

[26] Абдрешов С.Н. Биохимические показатели лимфы и плазмы крови у крыс при экспериментальном сахарном диабете / С.Н. Абдрешов, А.О. Балхыбекова, Э. А. Кырбасова [и др.] // Успехи современного естествознания, Москва, 2014, №3, с.183-184.

[27] Keleştimur H. Paratiroit hormonu ve kalsiyum-fosfat metabolizması. İçinde Ağar E, İnsan fizyolojisi.1. Basım. İstanbul Tıp Kitapevleri; 2021, p. 966-967

osteopathy and oxidative stress, indicators of the CSF system, and LFR from the breast lymph flow in both fluid environments of the animal. However, we decided to use lantus solostar, angioflux and vitamin D (cholecalciferol) together to bring the studied indicators to the level of normal limits. During the co-prescription of drugs in the treatment of DM modeled animals, it was observed that the sugar level decreased in both liquid environments compared to the corresponding indicators in the previous series of the study. During the study, the level of phosphorus in the blood and lymph decreased significantly in the blood compared to the lymph compared to the corresponding indicators in the previous series of the study. On the 45th day of the study, the baseline blood phosphorus level was 1.5% to 76.5% and 69.1% to 59.8% compared to the corresponding values of DM modeled animals, series III, IV and V. and up to 41.7%, and in lymph from 5.7% to 72.98% and from 60.7% to 53.8% % and decreased to 40.5%On the 30th day of the study, the concentration of Ca+2 in the blood increased from 3.9% to 41.4% and 50.5% compared to the initial indicator, DM modeled animals, III, IV and V series. from to 35.5% and to 13.7% decrease, in lymph from baseline to 35.2% and from 33.7% to 10.1% - and its increase up to 2.5% was determined[28,29].

It was determined that the level of PTH decreased in both liquid environments according to the increase of the study period. A decrease in the level of PTH in blood from 17.9% to 12.3% and 3.9% in comparison with the corresponding indicators of III, IV and V series on the 45th day of the study, and in lymph from 12.2% It was determined to decrease to 6.6% and 3.2%. The level of vitamin D increased in both liquid media depending on the duration of the study. The level of vitamin D on the 30th day of the study increased from 50.9% to 39.2% and 21.2% in the blood, from 67.1% to 25, compared to the corresponding indicators of the III, IV and V series. Its increase

[28]Дугушева В.А., Котова , Ю.А., Антакова Л.Н. Взаимосвязь риска развития сахарного диабета 2 типа и гиповитаминоза Д //Вестник новых медицинских технологий, Электронное издание – 2024, N 5, с.1-6

[29]Ефременко А.С., Крутикова Н.Ю. Патология костной ткани у детей с эндокринными заболеваниями// Вятский Медицинский Вестник, 2021, №1, с. 81-87.

to 8% and 13.5% was determined. The level of osteocalcin in the blood and lymph decreased depending on the increase in the study period in both fluid environments. On the 45th day of the study, during the co-administration of the drugs, the baseline level of osteocalcin in the blood was from 51% to 59.8% and from 45.5% to 34, compared to the corresponding indicators of DM modeled animals and III, IV and V series. 4% and 24.5% decrease, and in lymph from 6.7% to 56.6% and 40.9 Its decrease from % to 28.9% and 15.96% was determined. After the complex administration of drugs in the treatment of DM modeled animals, changes in the level of CAF system indicators in both liquid media were determined more during the study period, mainly in blood. During the study period, the decrease of fibrinogen level in blood was more clearly noticeable in both environments. On the 45th day of the study, the level of fibrinogen in the blood increased from 30.3% to 19.5% and 5.9%, and from 32.3% to 20.5% in the lymph compared to the corresponding indicators of the III, IV and V series. and its decrease to 7.7% was determined. On the 45th day of the study, it was determined that the level of PT in both fluid environments of the animal increased compared to the corresponding indicators of the previous series. That is, the blood level of PT on the 45th day of the study compared to the corresponding indicators of the III, IV and V series from 49.8% to 10.6% and 0.2%, from 53.6% in the lymph It was determined to extend to 25.8% and 4.9%. The level of thrombin time in the treatment of DM modeled animals after the complex determination of drugs on the 45th day of the study in comparison with the corresponding indicators of the III, IV and V series in blood from 51.8% to 27.7% and 11, 03% increase, increase from 64.5% to 42.3% and 14.4% in lymph has been determined. It was observed that PT and INR levels increased in both liquid environments according to the increase of the study period. PTT level increased from 50.2% to 29.3% and 18.5% in blood, from 52% to 26, in lymph compared to the corresponding values of III, IV and V series in both fluid media on the 45th day of the study. It was determined that it increased to 6% and 24.2%. The level of INR increased from 52.1% to 17.2% in blood and decreased to 7.9% in lymph compared to the corresponding values of series III, IV and V in both fluid media on the 45th day of the study,

and 146.2 % to 75.3% and to 57.2%. On the 45th day of the study, the level of the prothrombin index in both fluid environments of the animal compared to the corresponding indicators of the III, IV and V series increased from 24.3% to 4.8% and 2.4% in the blood and 25.9% in the lymph. decrease from to 9.8% and 1.9% was determined. Significant changes in the indicators of the antithrombotic system were also determined in the blood and lymph of rabbits after the complex administration of drugs in the treatment of DM modeled animals. On the 45th day of the study, the level of AT-III increased from 33.4% to 26.6% and 13.7% in blood compared to the corresponding indicators of III, IV and V series in both fluid media, and in lymph 34.9 Its increase from % to 23.2% and 15.2% was determined.

During the complex prescription of drugs in the treatment of DM, a comparative study of the changes in the level of CAF system indicators in both blood and lymph determines the continuous development in the direction of hypocoagulation during the research period. Normalization of lymph drainage functions of tissues is also observed as a result of complex treatment. As the research period increases, the difference of the studied indicators compared to the corresponding indicators in the previous series is more clearly noticeable.

Changes in the level of oxidative stress indicators in both fluid environments were observed in the blood compared to the lymph in the first stages of the study, that is, on the 5th day of the complex administration of drugs to DM modeled animals.

On the 45th day of the study, the level of MDA in both liquid media was from 2.3% to 62.8% in blood compared to the corresponding indicators of the initial, DM modeled animals, III, IV and V series, 50.9% to 36, 3% and decrease to 16.6%, from 10.2% to 63.4% in lymph, from 50.3% It was determined to decrease to 36.9% and 19.1%. As for the level of cataLFRe, after the complex administration of drugs to DM modeled animals, on the 45th day of the study, the level of cataLFRe in both liquid media increased from 5.7% to 66.9% in the blood compared to the corresponding indicators of the initial, DM modeled animals, III, IV and V series. up to 34.8%

to 19.4% and an increase of 3.5%, from 4.65% in lymph It was determined to increase to 67.8%, from 38.05% to 10.6% and 4.4%. During the complex administration of drugs for the treatment of rabbits with DM, on the 5th and 30th days of the study, LFR increased by 1.05 times (up to 4.91%, respectively) and 1.03 times (up to 3.91%, respectively) up to 2 %), a 1.03-fold decrease (up to 3.3 %), and a 1.45-fold decrease compared to the corresponding values of DM modeled animals (respectively up to 45.8%) increase was determined. After the complex prescription of drugs, on the 45th day of the study, the level of LFR increased by 1.04 times (up to 4.7%, respectively) compared to the indicator on the 5th day of the study. On the 45th day of the study, the level of LFR was 1.33 times (up to 33.5%, respectively) and 1.15 times (up to 15.1%, respectively) compared to the corresponding indicators of III, IV and V series. and increased by 1.05 times (up to 5.6%, respectively). A continuous increase of the level of LFR was observed compared to the corresponding indicators in the previous series of the study.

Thus, the complex administration of drugs for the treatment of rabbits with modeled CD significantly improved the lymphatic drainage function of tissues. The effect of this treatment was observed throughout the study and clearly showed itself in comparison with the corresponding indicators in the previous series of the study. Thus, during the complex prescription of drugs for the treatment of rabbits with DM modeled in the experiment, not only markers characterizing bone metabolism in the animal's blood and lymph,

The normalization of the levels of the CAF system and oxidative stress indicators, as well as the continuous increase of the LFR obtained from the breast lymph flow, compared to the corresponding indicators in the previous series of the study, were determined. This is also evaluated as a result of continuous normalization of lymph drainage properties of tissues. In conclusion, we conclude that there is a correlation between the changes in both fluid environments of rabbits modeled with DM in the experiment and the disruption of tissue lymphatic drainage. The combined use of lantus solostar, angioflux and vitamin D (cholecalciferol) in the treatment of DM animals allowed to obtain stable levels of sugar levels in blood and

lymph, markers of diabetic osteopathy and oxidative stress, indicators of the CAF system and LFR from breast lymph flow.

It was determined that the level of the indicators studied in both liquid environments of rabbits modeled by DM compared to the corresponding indicators in the previous series of the study continuously changed in the same direction. The detected changes corresponded to the level of diabetic osteopathy.

Thus, during the experiment, the treatment of modeled DM against the pathogenesis of this disease leads to an increase in the effect of the treatment. The combined treatment is also based on the normalization of the lymph drainage function of the tissues[30].

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RESULTS

1. During alloxan-induced diabetes in rabbits, the levels of sugar, markers of bone metabolism, the coagulation cascade, and oxidative stress in both humoral environments of the animals are altered, confirming the interaction between these systems. The weakening of LFR from the general thoracic lymphatic flow is a consequence of the functional deficiency of lymphatic drainage of tissues, which plays a role in the pathogenesis of diabetic osteopathy.
2. Oxidative stress and pathological changes in the coagulation cascade that develop during alloxan-induced diabetes in rabbits play an important role in the development of diabetic osteopathy, and the evacuation of extracellular fluid is delayed, resulting in a greater weakening of LFR than general thoracic lymph flow..
3. In the treatment of diabetic osteopathy in rabbits modeled with alloxan-induced diabetes, lantus solostar(insulin glargin) was administered to reduce blood and lymph sugar levels, as well as improve the levels of diabetic osteopathy markers, the CSF system, and oxidative stress indicators to normal compared to the corresponding values in previous series of the study, and a slight increase in LFR from the total thoracic duct was observed. .
4. The administration of angioflux(sulodexid) in the treatment of rabbits with a diabetes model had a positive effect on the indicators of the CAF system in the blood and lymph of the animals, stabilizing the levels of sugar, diabetic osteopathy markers, and oxidative stress indicators compared to the corresponding indicators in the previous series of the study, and increasing LFR from the general thoracic duct..
5. During the use of vitamin D (calciferol) in the treatment of diabetic osteopathy in animals with DM , in addition to a decrease in sugar levels in the blood and lymph of the animals, the levels of diabetic osteopathy markers, the LF system, and oxidative stress indicators approached the normal range

compared to the corresponding indicators in the previous series of the study, and LFR from the total thoracic duct increased..

6. For the first time, during the complex treatment of diabetic osteopathy consisting of lantus solostar(insulin glargin), angioflux (sulodexid) and vitamin D (calciferol), the levels of sugar, diabetic osteopathy and oxidative stress markers, indicators of the pulmonary system and LFR from the thoracic lymph flow in both humoral environments of the animals changed in the same direction and remained within normal limits, achieving a long-term therapeutic effect.

PRACTICAL RECOMMENDATIONS

1. During the treatment, it is necessary to take into account that there is a dynamic dependence between the level of sugar and the indicators of the CAF system and oxidative stress in the development of diabetic osteopathy.
2. In order to achieve a positive therapeutic effect during the treatment of diabetic osteopathy, it is necessary to take into account that the use of a complex treatment consisting of lantus solostar(insulin glargin), angioflux(sulodexid) and vitamin D(calciferol) , which have different mechanisms of action, eliminates disorders not only in the blood system, but also in the lymphatic system.
3. It is purposeful to propose the application of the drugs we used during the treatment of diabetic osteopathy in alloxan-induced diabetes modeled in rabbits in practical-experimental medicine.

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CONDITIONAL ABBREVIATIONS

DM- diabetes mellitus
WHO- World Health Organization
PTH- parathyroid hormone
MDA- malondialdehid
AOS- antioxydante system
AT-III- antithrombin III
PT- prothrombin time
PTT- partial thromboplastin time
İNR- International normalized ratio
Pİ- prothrombin index
TM- thrombin time
LFV- lymph flow velocity
CAF - coagulation anticoagulation fibrinolytic system
QDM- glucation end product
DIC- disseminated intravascular coagulation
BAM- biologically active substances HNE – 4-hydroxy-2-nonenol
UN- United Nations
GLUT(QNZ)- glucose transporter protein

The defense of the dissertation will be held on "29" May 2025 at "14⁰⁰" at the FD 2.07 Dissertation Council operating under the Azerbaijan Medical University.

Address: Az1024, Baku city, A. Gasimzade Street 14 (administrative building of Azerbaijan Medical University, 2nd floor, meeting hall of Scientific Council)

It is possible to get acquainted with the dissertation work in the library of Azerbaijan Medical University.

Electronic versions of the Dissertation and Abstract are posted on the official website of the Azerbaijan Medical University (amu.edu.az).

The abstract was sent to the necessary addresses in "23" April 2025.

Signed for print: 00.00.2025

Paper format: 60 x 84 1/16

Volume: 56379 characters
Order:228
Number of hard copies: 20
“Tabib” publishing house