AMERICAN ACADEMIC PUBLISHER

INTERNATIONAL JOURNAL OF MEDICAL SCIENCES

ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

EFFECT OF INTERLEUKINS IN DIABETIC PURULENT-NECROTIC WOUNDS AND ITS COMPLICATIONS

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ABSTRACT. Determination of biochemical processes, endogenous intoxication and histomorphological and planimetric indicators in purulent-necrotic lesions of the foot in an experimental way and in patients with purulent-necrotic processes in diabetes mellitus, the condition of the IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, and INF-γ system based on the dynamics of cytokine levels was studied. Complex surgical treatment of the drug Reomannisol corrects the balance of cytokines, allowing them to have an antioxidant effect on the cytokine system.

KEYWORDS:diabetic purulent-necrotic foot model, cytokine system, complex treatment, Reomannisol, Reosorbylact.

1. INTRODUCTION.

Diabetes mellitus (DM) is a chronic autoimmune disease. When purulent-necrotic lesions of diabetic heel syndrome appear, an inflammatory reaction appears and manifests itself in the form of a local reaction, which can lead to a systemic response[1,2,3,4]. As a result of bacterial action, under the influence of humoral factors, the activation occurs in the main phagocytosis cells – neutrophils (polymorphonuclear leukocytes), monocytes (macrophages), and platelets[5,6,7,8]. Activated cells begin to produce inflammatory mediators (cytokines) in the blood, which are involved in the regulation of vascular tone, hemostasis, and cell proliferation[3,9,10,11,12]. Atherosclerosis of blood vessels in patients with diabetes occurs 8-10 years earlier than in the general population. Therefore, an inflammatory reaction occurs against the background of changes in metabolism and circulatory disorders[13,14,15]. The pathogenetic mechanism of diabetes is complex, but the latest research data suggests that the participation of cytokines plays a large role in this disease. Cytokines are conditionally anti-inflammatory: natural immune regulators involved in inflammatory formation (IL-1, IL-2, IL-6, IL-12, TNF-α) and anti-inflammatory by pancreatic β-cells that depressant to insulin production: special immune regulators of inflammatory response (IL-4, IL-10, IL-13, INF-γ) these cytokines have protective and antidiabetic effects[16,17]. In addition, some cytokines regulate specific immune reactions (IL-2 and IL-4, transformative growth factor (TGF-β va et al.). It is involved in protein activation, differentiation, and growth of mature lymphocytes. Several cytokines (IL-1, IL-6, TNF-α, erythropoietin) can also have effects such as distension, which is simple hormones[18,19]. In addition, a similar single cell can secrete several different cytokines and the same cytokines at the same time, or different cells can produce several different or identical cytokines. Therefore, the importance of cytokines in the formation of diabetes mellitus, on the one hand, and in the formation of an inflammatory reaction, on the other, is interesting to obtain information about the state of the cytokine in patients with DFS[20]. The state of the cytokine system at the time of the development of purulent-necrotic processes in patients with DFS is completely unclear. Given the lack of research, DFS is solved by the dynamic state of the

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INTERNATIONAL JOURNAL OF MEDICAL SCIENCES
ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

cytokine system in patients with purulent-necrotic processes and the recurrence of purulent-necrotic processes[1,10,13]. It was decided to study the dynamics of cytokine levels in the blood serum of anti-inflammatory cytokines-interleukins IL-1β, IL-2, IL-6, IL-8, tumor necrosis factor-TNF-α, as well as gamma-interferon (IFN-γ) and anti-inflammatory interleukins IL-4, IL-10 patients. In our opinion, perhaps the imbalance of cytokines will help predict the course of the purulent-necrotic process and determine the tactics of surgical treatment[16,17]. In addition, the state of the cytokine balance is of interest in patients with recurrence of purulent-necrotic complications of DFS. Cytokine management balance is currently seen as a new direction of immunotherapeutic effects in the treatment of patients with purulent-necrotic lesions of DFS[18,19,20].

2. THE PURPOSE OF THE WORK.

Under experimental conditions, to determine the most effective ways of treating purulent-necrotic complications of the lower extremities in diabetes mellitus, taking into account pathogenetic features. Determination of the effectiveness of ozone therapy and its pathomorphological properties with new pharmacological drugs for the treatment of purulent necrotic process of the foot. By studying the dynamics of anti-inflammatory cytokine levels: analysis of the need and possibility of immunoprotection by studying cytokine status in IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, INF-γ patients on the development and recurrence of purulent-necrotic processes of DFS.

3. MATERIALS AND METHODS.

3.1. Determination of ozone concentration. To prepare an ozonated physiological solution, we ozonate 200,0 ml of physiological solution for 10 minutes at a concentration of 3-4 mg/l at a concentration of 3-4 mg/l and for 10 minutes in the apparatus "Medozons Beauty" (MEDOZONS LLC, Russia), then its dose is determined by the following formula:

D=C x V x t;

D – ozone concentration dose;
C – ozone concentration, mg/l;
V - oxygen exit rate, l/min;
t – time, min;

The purulent area of each rat is washed 3 times a day with ozonized physiological solution for 15-20 minutes.

3.2. Clinical stage. The concentration of cytokines in the blood plasma was determined using the StatFax 2100 immunological complex (manufactured by Cytokin LLC, St. Petersburg) by enzyme immunoassay (IFA). The obtained results are carried out using descriptive and non-parametric statistical methods on a personal computer with mathematical processing using Statistica 6.0 software (Table 1). Control parameters of the manufacturer's cytokine norms were used - the normative parameters obtained as a result of testing the donors were obtained from the manufacturer Cytokin LLC, St. Petersburg, Russian Federation. Plasma collection and cytokine level testing were performed on day 1 before surgery and on days 3, 5, 7, and 10 after surgery. The study was conducted in three phases and, accordingly, the patients were divided into 3 research groups: Group I (control group) - blood serum of patients with purulent-necrotic lesions of diabetes for the study of the cytokine system; II group (comparison group) - blood serum obtained during the treatment of patients with purulent-necrotic lesions of diabetes with ozone

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therapy and "reosorbilact" - 200.0 ml (YURIYA-FARM LLC, Ukraine); Group III (main group) - blood sera obtained during the treatment of patients with purulent-necrotic lesions of diabetes with ozone therapy and Reomannisol - 200.0 ml (REKA-MED FARM LLC, Uzbekistan).

Table 1. In normal patients, the amount of cytokines and the number of cells in the peripheral blood serum

Cytokines	**The concentration of cytokines in blood plasma, pg/ml**	**Production of cells in blood culture, pg/ml**	
		Spontaneous	**Induced**
IL-1β	0-50	0-50	1000-5000
IL-2	0	0	2-10 ED/ml
IL-4	0-50	30-50	100-400
IL-6	0-50	30-50	1000-3000
IL-8	0-50	30-100	1000-5000
IL-10	0-50	30-50	1000-3000
TNF-α	0-50	30-50	500-3000
INF-γ	0-10	10-100	1000-5000

Table 2. Characteristics of operations in group I

Type of operation	**Frequency of operations (n=60)**	
	abs.	**%**
Amputations at the hip level	20	33,3
Amputations at the lower leg level	6	10
Amputations at the foot level	12	20
Amputations at the level of the fingers	11	18,3
Amputations at the level of the fingers	7	11,7
Necrectomy	4	6,7

4. RESULTS.

4.1. Results of the clinical stage.

4.1.1. The first stage: to determine the imbalance of cytokines, consists of taking the blood plasma of 60 patients with purulent-necrotic lesions of diabetes and determining the amount of cytokines in it. 60 patients were treated at various levels in the Yiringli surgical department of the Yakkasaroy District Medical Association between 2021 and 2023. The age range of the patients was between 48-60 years. Neuropathic form of DFS - 25 people (type 1 DM - 2 patients, type 2 DM - 23): 12 were men and 13 women, and neuroischemic form of DFS - 35 patients (all with type 2 DM): 15 men and consisted of 20 women. The characteristics of operations performed in this group of patients are presented in Table 2. Most often, amputations were performed at the thigh level - 33.3%, heel area - 20%, finger level - 18.3%, necrotomy - 6.7%,

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ISSN NUMBER: 2692 - 5206 Volume 5,October ,2025

and sequestrectomy - 11.7%. Upper amputations were also performed as the main option, as a result of the failure of the approach to save vital organs: at the thigh level - in 33.3% of cases, and at the heel level - in 20%.

4.1.1A. Results and discussions in the first group. The dynamics of the level of cytokines in the first group are presented in Table 5. In the analysis of the indicators of the level of cytokines, the picture of growth was revealed: inflammatory cytokines: IL-1β, IL-2, IL-6, IL-8, TNF-α, and anti-inflammatory cytokines: IL-4, IL- 10, IFN-γ.

IL-1β: ranged from 7.25±0.24 to 2.9±0.1 pg/ml, but all changes were within the acceptable range. IL-1b appears in the blood plasma when a pathogenic agent enters the body for the first time or in autoimmune type 1 DM. Perhaps, with the first purulent-septic injury of DFS, the biological activity of this cytokine does not increase, that is, due to the insufficient activity of macrophages, monocytes, and lymphocytes due to the endothelial reaction, as well as the functional activity of fibroblasts decreases.

IL-2: ranges from 6.97±0.13 to 1.09±0.48 pg/ml, which is 3-2 times higher than normal values, especially in lymphocytes responsible for the immune system is explained by activation. In the postoperative period, the cytokine level decreases, but it is higher than the norm during discharge from the hospital, which allows us to consider this decrease as a residual reaction of the immune system, which can be associated with positive clinical dynamics.

IL-6: ranged from 90.1±0.76 to 12.59±1.9 pg/ml. A high level of cytokines on the first day, a decrease to normal by the 7th day, an acute phase with a decrease after the clinical relief of the inflammatory process, as well as an indirect reaction of the endothelial system in the purulent-necrotic focus indicate high protein activity.

IL-8: ranged from 129±0.13 to 579±0.11 pg/ml by day 7 and decreased to 51.8±0.11 pg/ml at hospital discharge, suggesting that indicates the presence of an acute purulent-necrotic process and the possibility of chronicity, since cytokine levels remain at higher levels during clinical recovery.

Table 5. Level of cytokines (in pg/ml) in patients of the first group

Cytokines/ Days	**Day 1**	**Day 3**	**Day 5**	**Day 7**	**Day 10**	Discharge (11-12 days)
IL-1β	7,25±0,24*	5,67±0,13*	4,56±0,1*	4,14±0,14*	2,9±0,1*	6,2±0,7*
IL-2	6,22±0,3*	6,97±0,13*	6,1±0,2*	6,5±0,15*	5,1±0,11*	1,09±0,48*
IL-4	235±0,13*	255±0,5*	280±0,12*	199±0,16*	101±0,1*	45±0,2*
IL-6	90,1±0,76*	80,5±0,6*	60±0,12*	16,02±0,23*	13±0,5*	12,59±1,9*
IL-8	129±0,13*	199,3±0,11*	245,5±0,1*	579±0,11*	65,7±0,15*	50,8±0,11*
IL-10	59,08±0,72*	58,12±0,3*	50±0,4*	51,68±0,73*	36±0,15*	6,65±1,33*
TFN-α	51,51±0	55±0,1	56±0,1	51,01±	40±0,1	2,2±0,52*

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	,7*	*	4*	0,94*	6*	
INF-γ	68,3±0, 1*	105,1± 0,14*	101±0, 11*	45,8± 0,13*	40±0,1 1*	10,4±0,14 *
Note:*– p<0,05.						

TNF-α: ranged to 56±0.14 pg/ml by day 5 and decreased to 2.2±0.52 pg/ml at hospital discharge. It shows the immunomodulatory and anti-inflammatory effects of the cytokine caused by the activation of macrophages, neutrophils, eosinophils, and endothelial cells, as well as the metabolic disorders associated with hyperglycemia.

IL-4: increased to 280±0.12 pg/ml by day 5 fluctuated between 235±0.13 pg/ml, and decreased to 45±0.2 pg/ml at hospital discharge. Such dynamics can be explained by the growth and activity of macrophages, lymphocytes, and, accordingly, a high level of anti-inflammatory cytokines. IL-4 performs regulatory functions.

IL-10: ranged from 59.08±0.72 to 6.65±1.33 pg/ml. It is an antagonist of anti-inflammatory cytokines and performs a regulatory function, reduces its level, and shows a favorable direction of this process with clinical improvement.

IFN-γ: fluctuated from 105.1±0.14 pg/ml to 10.4±0.14 pg/ml with a decrease on day 3. This dynamic can be explained by clinical recovery. IFN-γ has a wide spectrum of immunomodulatory activity, regulates and protects it, and establishes a balance of activity with fibroblasts, macrophages, and monocytes. In addition, on the first day, high levels of inflammatory and anti-inflammatory cytokines are observed, their number increases slightly, and on the fifth day, it decreases to a clinically favorable level. A high level of IL-8 indicates activation in response to acute inflammation and the possibility of the process becoming chronic. This stage of the research made it possible to study the state of the cytokine system in purulent-necrotic lesions of DFS.

4.2.1. The second stage: studying the dynamics of cytokines in recurrent purulent-necrotic lesions of diabetes.

4.2.1A. Materials and methods of the second stage - comparison group. The second group of the study included 40 patients (men and women aged 45 to 74). In 2021-2023, patients with DFS with recurrent purulent-necrotic lesions of diabetes were taken to the Department of Purulent Surgery of the Yakkasaroy District Medical Association. With the neuropathic form of DFS - 15 people: 5 men and 10 women and the neuroischemic form of DFS - 25 patients: 9 men and 16 women. The characteristics of operations performed in this group of patients are presented in Table 4. All patients, regardless of the severity of the disease, were treated locally with ozonized physiological solution, and 200.0 ml of Reosorbilact was administered intravenously once, the course of treatment was 7 days.

The number of operations is greater than the number of patients. This is explained by the fact that various operations were performed in one patient to preserve the quality of life and ability to work: necrotomy - 20%, amputation at the level of fingers - 22.9%, amputations at the level of the foot - 2.9%.

Table 6. Characteristics of operations in group II	
Type of operation	**Frequency of operations (n=40)**

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	abs.	%
Amputations at the hip level	23	65,7
Amputations at the lower leg level	0	0
Amputations at the foot level	2	5,0
Amputations at the level of the fingers	8	22,9
Amputations at the level of the fingers	5	14,3
Necrectomy	7	20

However, high amputations were performed when the tactics of saving vital organs were ineffective or when there was no prospect of saving the leg at the time of the initial examination - 65.7% (Table 6).

4.2.1B. Results and discussions in the second group. The dynamics of the state of the cytokine system in the blood plasma of patients in this group of patients are presented in Table 7. It should be noted that 1 day before the operation, only an increase in the level of IL-8 up to 182.7 pg/ml is detected. It increased to 245.5 pg/ml by day 5 and decreased to 60.9 pg/ml on days 11-12. The activity and level of IL-8 are considered to be related to the activity of IL-1β, IL-4, and TNF-α, as well as the effects of endotoxins on gram-negative bacterial microorganisms. In addition, IL-8-producing cells are monocytes, macrophages, T-lymphocytes, neutrophils, fibroblasts, keratinocytes, hepatocytes, endothelial cells, epithelial cells, and chondrocytes. IL-8 as a mediator stimulates chemotaxis of subpopulations of neutrophils, T-lymphocytes, and basophils; lysosomal enzymes activate neutrophils.

Table 7. Level of cytokines (in pg/ml) in patients of the second group

Cytokines/ Days	**Day 1**	**Day 3**	**Day 5**	**Day 7**	**Day 10**	Discharge (11-12 days)
IL-1β	10,2±0,2*	13±1,19*	7±1,12*	3,4±0,14*	5±1,1*	2,2±0,4*
IL-2	0	0	0	0	0	0
IL-4	32±1,14*	30±1,12*	31±1,11*	25±1,13*	17±1,4*	9±1,1*
IL-6	18,1±0,7*	15±1,2*	23±1,1*	15,02±1,3*	14,9±1,9*	10,59±1,9*
IL-8	182,7±1,1*	201,5±1,1*	245,5±1,3*	210,1±1,2*	103,7±1,4*	70,9±1,9*
IL-10	9,08±0,7*	23,1±0,9*	19,3±0,8*	10,68±1,3*	14,5±1,1*	15,65±1,2*
TFN-α	21,5±1,14*	19,6±1,11*	15,6±0,9*	14,1±0,1*	12,5±1,1*	10,2±0,5*

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INF-γ	0,9±1 ,1*	2,6±1, 1*	1,1± 1,3*	8,1±1, 1*	0,8±1, 1*	0,3±0,9*
Note: * – p<0,05.						

In addition, it has receptors that react with monocytes and neutrophils, which can cause a specific appearance, and stop these cells in the capillaries located in the area of inflammation. Such a high level of IL-8 indicates that the inflammatory process in the leg becomes chronic in a positive way. The dynamics of cytokine levels are more clearly shown in Figure 2. At the same time, changes in the level of IL-1β, IL-2, IL-4, IL-6, IL-10, TNF-α, and INF-γ cytokines were noted, but within normal limits. Locally, in 2 cases, variants of purulent-necrotic injuries, which included not only two anatomical areas of the leg, but also the spread of the process to the border of the upper and middle third of the leg, and in 3 cases - ended with gangrene of the distal parts of the leg. Cytokine regulation of the inflammatory reaction is insufficiently activated in patients with chronic DFS and secondary immunodeficiency with recurrence of the purulent-necrotic process. This leads to a lack of growth factors and slow healing. Perhaps this condition can be considered as a weak proliferative response. Accordingly, as a local process, the functional status of functional mononuclear phagocytes, platelets, macrophages, fibroblasts, keratocytes, endothelial cells, and other cells slows down with slow resorption of the infiltrate and the formation of necrosis.

4.2.1C. Materials and methods of the third stage – main group. Taking into account the information obtained about the state of the cytokine system in patients with purulent-necrotic processes of DFS, it was decided to study the antioxidant effect of ozone therapy and the drug Reomannisol. The research group consists of 40 patients. With the neuropathic form of DFS - 16 people: 4 men and 12 women, and the neuroischemic form of DFS - 24 patients: 8 men and 16 women, aged 50 to 75 years. In the anamnesis, there were multiple recurrences of purulent-necrotic complications (from 2 to 4 times). The duration of diabetes is from 5 to 20 years. The goal of surgery and conservative treatment algorithms is to preserve the function of the leg or reduce the level of amputation. Reomannisol was used from the first day of hospitalization to study the antioxidant and peripheral blood circulation effects of the drug in complex treatment. According to the scheme, 200.0 ml of solution was administered intravenously 1 time per day for 10 days. Plasma sampling and cytokine levels were performed on the first day before and/or after surgery, and then on days 3, 5, 7, 10, and 12 again blood plasma was taken and the level of cytokines was determined.

4.2.1D. Results and discussions in the third group. Table 8 lists the procedures performed in patients of group III.

Table 8. Characteristics of operations in group III

Type of operation	**Frequency of operations (n=35)**	
	abs.	**%**
Amputations at the hip level	10	28,6
Amputations at the lower leg level	1	2,9
Amputations at the foot level	1	2,9
Amputations at the level of	15	42,8

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the fingers		
Amputations at the level of the fingers	11	31,3
Necrectomy	15	42,9

Operations performed to save the leg: necroctomies - 42.9%, sequestrectomy - up to 31.3%, amputations at the level of toes - 42.8%, amputations at the level of the heel - 34.3%. In addition, the number of high amputations: at the hip level - 28.6%, and at the heel level - 2.9%. Compared to the second group, the number of upper amputations decreased from 65.7% to 28.6%. In addition, the antioxidant effect of Reomannisol manifested in the induction of inflammatory and anti-inflammatory cytokines, was determined. Cytokine levels in patients of study group III are presented in Table 9

Table 9. The number of cytokines after ozone therapy + Reomannisol treatment in group III patients, pg/ml

Cytokines/Days	**Day 1**	**Day 3**	**Day 5**	**Day 7**	**Day 10**	Discharge (11-12 days)
IL-1β	64,59±3,3*	74,48±1,9*	95,27±2,2*	71,48±1,8*	31,49±1,9*	20±1,8*
IL-2	1,2±0,3*	1,7±0,13*	1,1±0,2*	0,54±0,15*	0,2±0,11*	0
IL-4	41,56±2,3*	43,96±3,1*	39,29±4,1*1	30,7±3,2*	32,9±3,5*	20,58±2,2*
IL-6	228,92±5,1*	138±3,2*	50,8±2,1*	42,6±3,1*	38±2,1*	8,5±1,1*
IL-8	181,14±4,1*	197,31±3,1*	245,47±5,9*	222,6±4,5*	109,6±5,1*	53±1,1*
IL-10	48,8±2,8*	25,81±1,6*	34,2±2,1*	40,2±3,2*	38,7±2,5*	21,2±1,3*
TFN-α	147,86±4,6*	150,6±5,3*	121,96±5,4*	91,58±4,3*	41,1±2,1*	21,87±1,1*
INF-γ	194±3,4*	205,9±6,5*	89±4,1*	47,8±2,1*	7,8±0,4*	5,39±0,3*

Note: * – p<0,05.

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IL-1β: high level of cytokine up to 64.59±3.3 pg/ml on the first postoperative day, increased to 95.27±2.2 pg/ml on the fifth day and decreased to 20 ± 1.8 pg/ml. IL-1b promotes the proliferation of monocytes, macrophages, neutrophils, endothelium, smooth muscle cells, fibroblasts, keratinocytes, T- and B-lymphocytes, along with other cytokines; increases the stimulation of receptors for IL-2; activates endothelial cells; induces an acute phasic response.
IL-2: increases to 1.2±0.3 pg/ml on the first postoperative day, to 1.7±0.13 pg/ml on the third day, and 0 at discharge. After an increase in IL-2, the active implementation of the immune response and the activation of T cells show.
IL-4: fluctuations were noted within normal limits and an increase was observed in only one case, that is, 76 pg/ml in a patient with an allergic background, which increased due to the development of postoperative traumatic dermatitis on the limbs after surgery. Reomannisol may stimulate the production of this cytokine by mononuclear cells in the peripheral blood of allergic patients. However, as a result of antioxidant activity, there are fluctuations in the group of cytokines with pro-inflammatory effects, but only within normal limits.
IL-6: a high level of cytokine up to 228.92±5.1 pg/ml was recorded on the first postoperative day. Then it gradually returned to normal, and by the time of discharge from the hospital, it was back to normal. IL-6 is produced by T-lymphocytes, monocytes, macrophages, and fibroblasts. Hematopoiesis causes the differentiation of progenitor cells, stimulates the development and production of megakaryocytes, promotes the growth and differentiation of platelets, T- and B-lymphocytes, and stimulates the production.
IL-8: peak cytokine levels increased to 181.14 ± 4.1 pg/ml on the first postoperative day, 245.47 ± 5.9 pg/ml on the fifth day, and 53 ± 1.1 pg/ml at hospital discharge. decreased to ml. As revealed in the study of the previous two groups, the growth of this cytokine characterizes the transition of the process to a chronic form.
IL-10: An anti-inflammatory cytokine produced by T-lymphocytes, macrophages, keratinocytes, and B-lymphocytes. It blocks the functional activity of macrophages and the production of anti-inflammatory cytokines by monocytes and macrophages. It increases the proliferation of B-lymphocytes and the secretion of immunoglobulins IgE. However, IL-10 can stimulate the synthesis of IL-4 in a balanced state. By preventing the systemic response to the inflammatory process, IL-10 ensures a balanced level of inflammatory and anti-inflammatory cytokines and controls the immune response, which has a positive effect on the prevention of purulent-necrotic recurrence.
TNF-α: produced by macrophages, monocytes, keratinocytes, T-lymphocytes, B-lymphocytes, neutrophils, and endothelial cells. TNF-α has a variety of effects, occurs due to the modulation of the expression of genes for cell growth factors, cytokines, transcription factors, cell surface receptors, and acute phase proteins, and plays an important role in protection against them. The increase of this cytokine on the third day up to 150.6±5.3 pg/ml after the operation is included in the high activity and the cytokine itself.
INF-γ: on the first day, a high level was recorded to 194±3.4 pg/ml, on the third day it increased to 205.9±6.5 pg/ml and decreased to 5.39±0.3 pg/ml, this indicates its immunomodulatory value and involvement in the regulation of the anti-inflammatory response.

5. CONCLUSION.

1. The best option for creating an experimental model of a diabetic foot is the introduction of alloxan intraperitoneally in a single dose of 12 mg per 100 g, in which moderate diabetes develops.

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2. After using the drug Reomannisol intraperitoneally at a dose of 1 ml / 100 g 1 time per day for 5 days, there was a sharp decline in EI numbers. On the 10th day, the EI values in the experimental group returned to normal, similar to those in the intact group. The drug Reomannisol performs "biochemical rehabilitation", due to its inherent qualities: antioxidant, improves blood rheology, detoxification, and diuretic. In rats of the control group, the EI numbers remain at high levels until the end of the experiment.

3. The rate of healing of wound defects in rats with diabetic foot syndrome in the control group falls on the 14th day since the terms of resorption and rejection of necrotic tissues in the wound are lengthened, damage to the vessels of the microvasculature (microangiopathy), edema is observed for a long time. The wounding process against the background of DM is characterized by the late formation of angiogenesis, slowing down and impaired maturation of granulation tissue, and marginal epithelialization. In the experimental group, in rats, along with the local traditional method of wound treatment, the drug Reomannisol was used intraperitoneally, as a result, wound healing was recorded on the 10th day from the moment the wound was applied to the foot of the rats. The use of local treatment and Reomannisol can enhance angiogenesis in the early stages of the experiment and restore disturbed microcirculation (neoplasms of blood vessels), increase macrophage response, fibroblast proliferation, maturation and remodeling of granulation tissue and its epithelization, reduce the inflammatory reaction, which leads to more effective and early healing wound area.

4. Comprehensive treatment (application of a local traditional method of treatment on the wound and the drug Reomannisol) in an experimental model of the diabetic foot has positive effects on reparative processes and wound healing, due to the formation and enhancement of angiogenesis, as well as on the functional parameters of vital organs by reducing intoxication organism.

5. In the case of purulent-necrotic processes in DFS, the adequate introduction of the cytokine system is characterized by the slowing down of the local process, corresponding to acute inflammation, but increases the tendency of the process to go into a chronic state. With the recurrence of purulent necrotic inflammation, there is a synchronization of the process and a secondary immune deficiency, which does not allow the cytokine system to adequately join the anti-inflammatory system. Reomannisol allows us to consider it a physiologically active compound with clear antioxidant activity.

6. Reomannisol has an antioxidant effect on the cytokine system, correcting the cytokine balance. It can decrease the function of pro-inflammatory and anti-inflammatory cytokines, and interferons. Reomannisol is effective in preventing the recurrence of purulent-necrotic lesions of DFS in conditions of secondary immunodeficiency, so it is a necessary drug in the main therapy complex.

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