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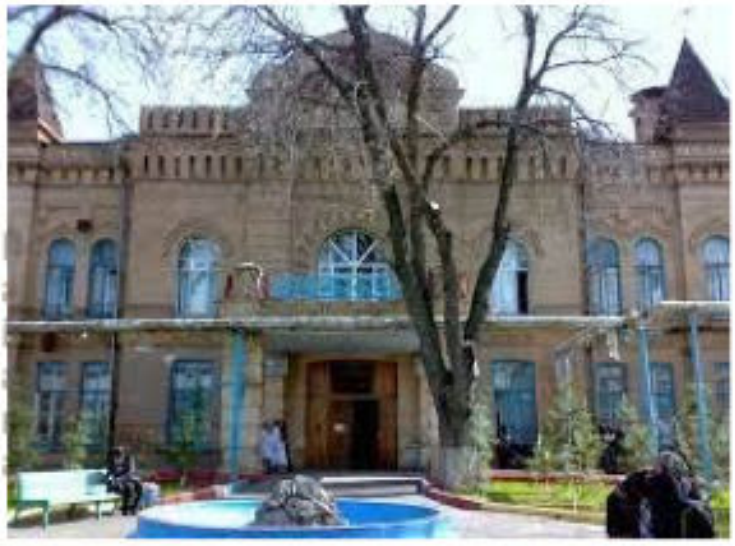

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New Approaches to the Treatment of Ulcerative-Necrotic Lesions of Diabetic Foot Syndrome

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ABSTRACT

Background. In recent years, the use of cytokines and various growth factors in the treatment of chronic wounds in patients with diabetes mellitus has been of great interest. This manuscript is devoted to this particular problem, which made it possible to improve the results of treatment.

Material and methods. The results of the treatment of 72 patients with type 2 diabetes mellitus with diabetic foot syndrome are presented, consisting of two groups: the main group (38 patients who, along with the standard treatment of diabetic foot syndrome, underwent local applications with a solution of the immunomodulator Superlymph according to the generally accepted scheme) and the comparison group (34 patients who used traditional treatment for this pathology). Clinical, laboratory and instrumental research methods available in clinical settings were used.

Results and conclusions. A change in the local cytokine status in the form of a decrease in anti-inflammatory and an increase in pro-inflammatory cytokines is characteristic of patients with diabetic foot syndrome. The levels of cytokines of wound discharge exudate depend on the duration of diabetes mellitus, and the level of glycated haemoglobin and leukocytosis and do not depend on the form of diabetic foot syndrome. The use of Superlymph in the complex therapy of patients with diabetic foot syndrome contributes to the normalization of the immune status, which in turn ensures effective healing of ulcerative foot defects in diabetic foot syndrome.

Keywords: Type 2 diabetes mellitus, diabetic foot syndrome, cytokines, cytokine therapy

INTRODUCTION

According to the World Health Organization, there are currently about 180 million patients with diabetes in the world. Calculations have shown that, if the average life expectancy increases to 80 years, the number of patients with diabetes mellitus can reach 17% of the total population [1, 3, 4, 31].

In developed industrial countries, the incidence of diabetes mellitus ranges from 1% to 6% of the total population [22,24].

Given the chronic incurable course of the disease and the increasing average life expectancy of patients, research aimed at developing methods for diagnosing, preventing, and treating late complications of diabetes mellitus is becoming increasingly relevant [23, 30]. One of the complications of diabetes mellitus, which most often leads to disability and a decrease in the quality of life of patients, is diabetic foot syndrome [7, 10, 11, 14, 18].

Diabetic foot syndrome is observed in 10-30% of patients with diabetes mellitus [9, 19-21]. Amputations of

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the lower limbs in this group of patients are performed 20 times more often than in the rest of the population. The number of large amputations in purulent-necrotic complications of diabetic foot decreases slowly and accounts for 30-35% of all patients with diabetes mellitus [8, 32, 33, 36]. The prognosis is even more depressing when you consider that almost every second patient after amputation in 3-4 years has to amputate another limb. According to many authors, with a timely approach, high amputations in purulent-necrotic complications of diabetic foot syndrome could be prevented in 85% of cases [25, 37, 38].

In recent years, new data have appeared on the pathogenesis of diabetic micro- and macroangiopathy, and neuropathy. If earlier it was traditionally considered the trigger mechanism and the main factor in these processes of carbohydrate metabolism disorders, then from modern positions, immune mechanisms began to play a significant role in the pathogenesis of diabetic foot syndrome [15].

According to numerous data, diabetic foot syndrome is characterized by changes in the immune system that are diverse in terms of points of application and depth - a decrease in the number and activity of T-lymphocytes, a violation of the phagocytic link, as well as an imbalance of cytokines: an increase in pro-inflammatory cytokines and a decrease in anti-inflammatory cytokines [27, 29].

Cytokines, being universal regulators of cellular functions, are secreted by all types of cells: lymphocytes, monocytes, macrophages, neutrophils, epithelial cells, and fibroblasts. Their highly specific receptors on binding cells form a single cell-mediator chain involved in the development of the immune response, as well as the processes of inflammation and regeneration, however, the content of cytokines in the discharge of the wound in diabetic foot syndrome has not been studied [27, 29].

The development of immunodiagnostic methods and the emergence of new immunomodulators makes it possible today not only to identify the level of defect in the immune system, but also to carry out targeted immunocorrection.

In recent years, the use of cytokines and various growth factors in the treatment of chronic wounds in patients with diabetes mellitus has been of great interest. Growth factors regulate the synthesis of collagen and connective tissue matrix components, vascular growth and re-epithelialization.

All of the above substantiates the relevance of the problem and the feasibility of the study in order to study the possibility of using cytokines and growth factors in patients with diabetic foot syndrome.

MATERIALS AND RESEARCH METHODS

The present study included 72 patients with type 2 diabetes mellitus with diabetic foot syndrome, who made up two groups: the main group and the comparison group. The main group included 38 patients who, along with the standard treatment of diabetic foot syndrome, underwent local applications with a solution of the immunomodulator Superlymph according to the generally accepted scheme. The comparison group consisted of 34 patients who used traditional treatment for this pathology.

Of the 72 patients included in the study, 43 (63.5%) were women and 29 (36.5%) were men. The age of the patients ranged from 52 to 78 years, the average age of the patients of the main group was 66±7.9 years, and the comparison group was 65.4±6.6 years. The duration of type 2 diabetes mellitus in patients of the main group averaged 11.5±6.2 years, and the comparison group - 12±6.3 years. All patients underwent drug therapy for diabetes mellitus before hospitalization: 31 patients (43%) received insulin therapy, 17 patients (23.6%) received oral hypoglycemic drugs, and 24 patients (33.4%) received combination therapy. The mean level of glycated haemoglobin (HbA1c) in the study group was 10.5±1.4%, and in the comparison group - 10.5±1.2%.

Of the concomitant diseases, coronary heart disease prevailed in 63 (87.5%), hypertension in 55 (76.5%) people, and chronic pyelonephritis in 43 (60%). In 54 (75%) patients, the presence of obesity of 1-3 degrees was revealed. The body mass index in the patients of the main group was 32.5±4.4, in the comparison group - 32.7±5 ($p>0.05$). Other complications of diabetes mellitus were also identified: diabetic retinopathy in 29 (40.3%), and diabetic nephropathy in 26 (36%).

Taking into account the specifics of the hospital and the goals and objectives of our study, the study included patients with neuropathic and neuro-ischemic forms of diabetic foot syndrome and with 3rd degree of foot damage according to Wagner [35].

The exclusion criteria for the study were patients with other forms and stages of diabetic foot, severe concomitant diseases (acute circulatory failure, dementia, oncology, myocardial infarction), and the need for emergency surgical treatment.

In the main group, 25 (34.7%) patients were diagnosed with a neuro-ischemic form and 13 (18.1%) with a neuropathic form of diabetic foot syndrome, in the com-

parison group, 23 (30.6%) with a neuro-ischemic form, and 11 (16.6%) with a neuropathic form.

The duration of persistence of diabetic foot syndrome was 18.4±12 months in patients of the main group and 21±10.5 months in the comparison group ($p>0.05$). The presence of a peptic ulcer defect was first diagnosed in the period from 2 to 20 months after the onset of symptoms of diabetic foot syndrome in patients of the main group, from 1 to 21 months in patients in the comparison group.

The area of the ulcer defect in patients of the main group averaged 2.7±1.9 cm^2, and in the comparison group - 2.9±1.4 cm^2, the depth of the ulcer defect in the main group averaged 2.9±1.8 mm, in the comparative group - 3.1±1.4 mm.

The methods of the clinical study were comprehensive and included: a standard survey taking into account the anamnesis of complaints, anamnestic data and physical examination. When examining the lower extremities, attention was paid to the colour of the skin, the presence of oedema, the temperature of the skin, and the presence of hyperkeratosis and deformities. Upon admission and in dynamics, the area and depth of the ulcerative defect were measured, and the presence of local signs of infection was recorded.

Laboratory research methods consisted of determining: the level of glucose in capillary blood was determined using standard test strips on the glucometer "Glucotrend" (Boehringer Mannheim Roche) (Austria); the level of glycated haemoglobin was determined on the DCA-2000 device by latex inhibition of immunoagglutination using the Hemoglobin Ale Reagent kit.

All patients underwent an immunological study of the level of pro- and anti-inflammatory cytokines (IL-8 and TGF-β) in the blood serum and exudate of wound discharge of ulcerative defect before and after treatment. The material was taken from the purulent-necrotic focus with 1.0x1.0 cm filter paper, which was then placed in a 1.5 ml Eppendorf tube in 100 μl of sterile saline, after 30 minutes the filter paper was removed and the contents of the tube were frozen for further storage for a month.

Determination of the level of cytokines was carried out by enzyme-linked immunosorbent assay using test systems manufactured by BIOSOURCE (Belgium). Test systems are microplates coated with antibodies to the antigen - the cytokine structure under study, in our case IL-8 and TGF-β.

All patients underwent bacteriological examination of the local microflora of the ulcer defect and its sensitivity to antibiotics with the determination of a quantitative content of 1 gram of tissue.

For the diagnosis of peripheral sensorimotor neuropathy, a generally accepted comprehensive neurological clinical and instrumental examination was performed, including an assessment of the neurological symptom scale - NSS (Neuropathy Symptom Score or neuropathic symptomatic score) and the sign scale - NDS (Neuropathy Disability Score or neuropathic dysfunctional score).

The severity of peripheral sensorimotor neuropathy was assessed on the basis of a study of the thresholds of 4 types of sensitivity (tactile, pain, temperature and vibration) and a study of reflexes (Achilles and knee) based on standardized tests accepted in international practice for the study of peripheral sensorimotor neuropathy.

The threshold of vibration sensitivity was investigated using a graduated neurological tuning fork vibrating at a frequency of 128 Hz. Vibration sensitivity was determined at the apex of the first toe and on the medial malleolus. Temperature sensitivity assessment was carried out using a Tip-term device. To determine tactile sensitivity, a standard monofilament was used to examine the lower extremities, creating a pressure of 10 grams on the skin. To study pain sensitivity, an "English" pin was used to recognize the patient's touch of a sharp and blunt object.

For the study of Achilles and knee reflexes, a neurological hammer was used, with an assessment of them as normal, weakened, absent.

Doppler ultrasound was performed on the EUB HITACHI device. The degree of hemodynamic disturbance of the preserved limb was determined by the size of the brachial-ankle index. The brachio-ankle index was calculated as the ratio of the systolic pressure in the artery of the lower limb to the systolic pressure in the brachial artery.

All patients underwent an X-ray examination of the feet and ankle joints in two projections.

All patients underwent insulin therapy under the control of glycemic indicators, antibiotic therapy.

In patients with ulcerative defects with rough hyperkeratosis edges, the wound was cleaned mechanically with a scalpel, then the ulcerative defect was washed with a liquid antiseptic (0.5% solution of Dioxidine, 0.01% solution of Miramistin, or solution of Chlorhexidine). After treatment of the ulcerative defect, an atraumatic bandage was applied to the wound. Since the patients we observed were in the first stage of the wound process, dressings with water-soluble ointments (Levomekol or Dioxycol) were used in the patients of the

comparison group. Patients of the main group underwent dressings with Superlymphoma, which is a standardized complex of cytokines, among which the activity of IL-1, 2, 6, tumor necrosis factor-a (FNO-a), factor inhibiting phagocyte migration, TGF-β was determined.

In our study, we used lyophilized Superlymph powder: 1 ampoule of dry matter of the drug was diluted in 2 ml of 0.9% sterile saline solution and applied locally to the wound in the form of applications 1 time per day for 7 days.

The criteria for evaluating the effectiveness of therapy were clinical (dynamics of subjective and neurological symptoms, eradication of pathogens from the focus of inflammation, dynamics of the wound process and local status, length of hospital stay), laboratory (changes in the peripheral blood formula, changes in biochemical parameters) and immunological parameters (cytokine levels). Evaluation of the effectiveness of treatment was carried out immediately after treatment.

Statistical data processing was carried out using the statistical package of the Statistica vers program. 6 and MS EXCEL spreadsheets version 2003 using standard parametric methods of variation statistics.

RESULTS AND DISCUSSION

Results of clinical and laboratory-instrumental examination.

In all patients, the following complaints were detected before treatment: pain in the feet (97%), weakness in the legs and fatigue (94%), paresthesia (98%), and cramps in the calf muscles (87%). When assessing clinical symptoms on the Neurological Symptom Scale (NSS), the vast majority of patients (76.4%) had severe neuropathy (7-9 points). An analysis of the severity of objective manifestations of diabetic neuropathy on the NDS scale showed that a significant number of patients 63 (87.5%) had severe neuropathy, which confirms the presence of foot ulcerative defects in all patients we observed.

In all patients, changes in clinical and laboratory data were noted before the treatment measures.

All patients of the observed groups with diabetes mellitus were in the stage of decompensation, as evidenced by significant increases in fasting blood glucose (10.8±1.1 mmol/L in the main group and 11.3±1.7 in the comparison group) and the level of glycated haemoglobin (HbA1c) (10.5±1.4% in the main group and 10.5±1.2 in the comparison group). In addition, in 52 (72.2%) patients, glycosuria was determined in the study of urine, and ketonuria was detected in 11 (15.3%) patients.

X-ray examination of the feet and ankle joints revealed diffuse osteoporosis in 41 patients (57%), focal osteoporosis in 12 (16.7%), deforming osteoarthritis in 12 (16.7%), focal and marginal destruction in -18 (25%), in 7 patients (9.7%) no bone-destructive changes were detected.

In order to obtain information about the presence of stenotic lesions of the arteries of the lower extremities, a study of the shoulder-ankle index was performed on all patients. In the neuro-ischemic form of diabetic foot syndrome, the average value of the brachio-ankle index was 0.8±0.1, which coincides with the data of most authors, indicating a decrease in the brachio-ankle index to 0.8-0.7 with ischemic damage to the arteries of the lower extremities. We did not identify any patients with a brachio-ankle index of less than 0.6, which would be regarded as critical ischemia and would require surgical intervention. In the neuropathic form of diabetic foot syndrome, the average value of the shoulder-ankle index was 1.1±0.2, which also coincides with the values characteristic of this form of diabetic foot syndrome (1.1-1.3). In 13 (19%) patients with neuropathic diabetic foot syndrome, the shoulder-ankle index was within normal limits.

Changes in Doppler ultrasound were detected in all 47 (66%) patients diagnosed with the neuro-ischemic form of diabetic foot syndrome and only in 7 (9.7%) patients with the neuropathic form of diabetic foot syndrome. In patients with the neuropathic form of diabetic foot syndrome, an increase in the speed of retrograde blood flow was revealed, which is characteristic of this form of diabetic foot syndrome. In 25 (53%) people with a neuro-ischemic form of diabetic foot syndrome, a decrease in the average blood flow velocity through the main vessels of the lower extremities were revealed, in 32 (68%) patients, peripheral arterial occlusion of various calibres was detected: at the level of a. femoralis in 2 (7.7%) patients, at the level of a. poplitea in 19 (61%), at the level of a. tibialis post., in 11 (31%). In 5 (7%) patients with a neuropathic form of diabetic foot syndrome, stenosis of the arteries of the lower leg and foot was also revealed, which practically did not disrupt the main blood flow.

Analysis of the content of cytokines (IL-8 and TGF-β) in the blood serum and exudate of wound discharge in patients with diabetic foot syndrome.

We investigated the level of the pro-inflammatory cytokine IL-8 and the anti-inflammatory cytokine TGF-β since it is these cytokines that play a special role in the pathogenesis and development of chronic ulcerative de-

fects: IL-8 has pronounced pro-inflammatory properties, the main biological effects, which are the induction of neutrophil chemotaxis, the subpopulation of T-lymphocytes and basophils, the activation of neutrophils to the release of lysosomal enzymes, the "respiratory explosion" and degranulation, thereby intensifying and prolonging the inflammatory process [12]; TGF-β is a cytokine with anti-inflammatory properties that inhibits the activity of natural killer cells, reduces the proliferation of B and T lymphocytes and many cell types, stimulates reparative processes, promoting wound defect healing [2].

In the study of the level of IL-8 in the blood serum in 14 (20%) patients, we found extremely low concentrations of 5.2±0.5 pg/ml, in 58 (80%) patients the values of IL-8 in the serum were not determined at all. In the study of the level of TGF-β in the blood serum in 46 (64%) patients, we found average concentrations equal to 475.5±43.5 pg/ml, while in 26 (36%) patients, as in the case of IL-8, TGF-β in serum was not detected.

The average concentration of IL-8 in the exudate of wound discharge in patients with diabetic foot syndrome was 2127.54±89.3 pg/ml, which is more than 400 times higher than the concentration of this cytokine in the same patients in the blood serum. The average concentration of TGF-β in the exudate of wound discharge was 1360.6± 566.5 pg/ml, which is 3 times higher than the concentration of this cytokine in the blood serum. The data obtained confirm that the predominant production of the pro-inflammatory cytokine IL-8 is induced in the exudate of the wound discharge of trophic ulcers in diabetes mellitus, while the anti-inflammatory TGF-β is characterized by lower production.

Thus, we confirmed the data that in many cases the determination of the local cytokine status of biological fluids (wound discharge exudate) is more informative than its systemic determination in the blood serum. Probably, cytokines, as short-range molecules, practically do not enter the systemic circulation during the immune response but are released and sold directly in the focus of inflammation. In this regard, it seems promising to study the local content of cytokines in the tissues of the body, where the influence of systemic factors in the regulation of immunity from the nervous and endocrine systems has a lesser effect [28].

It is known that in many cases the determination of cytokines in biological fluids is more informative than its determination in blood serum [13]. In particular, with the development of a local inflammatory process, which we observe in our work, or with a violation of the mechanisms of tissue regeneration, when there are no pronounced changes in the systemic immune response. In this regard, later in our work, we investigated and compared the levels of cytokines only in the exudate of wound discharge from trophic ulcers.

When analyzing the data on the content of the studied cytokines in the exudate of the wound discharge, there were no statistically significant differences in cytokine levels in neuropathic and neuro-ischemic forms of diabetic foot syndrome ($p>0.05$).

Neuropathy and angiopathy in diabetes mellitus contribute to the violation of tropism in tissues, which sooner or later leads to the formation of ulcerative defects [17]. However, the further course of the ulcerative process, is determined not only by the form of diabetic foot syndrome, but also by the state of the immune system. Changes in the immune status are determined by the presence of diabetes mellitus as such and, therefore, are unidirectional in different forms of diabetic foot syndrome [16].

A positive correlation was established between the duration of diabetes mellitus and the baseline level of pro-inflammatory IL-8 ($g=0.84$, $p<0.05$ in the main group, $g=0.81$ $p<0.05$ in the comparison group) and a negative correlation between the duration of diabetes mellitus and the baseline level of TGF-β ($r=-0.77$, $p<0.05$ in the main group, $r=-0.84$, $p<0.05$ in the comparison group). Similar correlations were found between the levels of glycated haemoglobin (HbA1c) and the cytokines studied: a positive correlation between IL-8 and HbA1c ($r=0.44$, $p<0.05$ in the main group, $r=0.74$, $p<0.05$ in the comparison group, a negative correlation between TGF-β and HbA1c ($r=-0.38$, $p<0.05$ in the main group, $r=-0.76$, $p<0.05$ in the comparison group).

Thus, the longer the duration of diabetes mellitus, as well as the higher the level of glycated hemoglobin and thereby the pronounced decompensation of diabetes mellitus, the more significant the changes in the immune system in patients, in particular, cytokine imbalance - an increase in pro-inflammatory and a decrease in anti-inflammatory cytokines.

A correlation analysis was also carried out between the levels of the studied cytokines (IL-8 and TGF-β) and the levels of leukocytes, neutrophils and erythrocyte sedimentation rate, and the following relationships were revealed: in all patients of the observed groups, a positive relationship between the level of IL-8 and the level of leukocytosis was detected before treatment ($g=0.85$, $p<0.05$ in the main group, $g=0.78$, $p<0.05$ in the comparison group), a negative relationship between the level of

TGF-β and the number of leukocytes and neutrophils was detected only in patients of the main group (r=-0.78, p<0.05; g-0.46, p<0.05, respectively). There was no association between cytokine levels and erythrocyte sedimentation rate before treatment.

Evaluation of the effectiveness of Superlymph in patients with diabetic foot syndrome in type 2 diabetes mellitus.

The criteria for evaluating the effectiveness of therapy were clinical, laboratory and immunological indicators, which were evaluated before and immediately after the treatment.

Correction of carbohydrate metabolism was one of the main tasks of the therapy carried out in both clinical groups. The prescribed adequate insulin therapy made it possible to significantly (p<0.01) reduce the level of glycated haemoglobin and fasting blood glucose in both clinical groups, blood glucose after meals in the comparison group did not significantly decrease. Comparing these indicators after treatment, we found that in the main group, these indicators significantly decreased more than in the comparison group. In order to exclude the positive effect of diabetes mellitus compensation on the dynamics of the treatment of patients in the main group and to equally compare the effectiveness of the therapy in both study groups, regardless of the indicators of carbohydrate metabolism, we took from the main group of patients who, after treatment, did not differ from the corresponding values of patients in the comparison group. It was in these patients of the main group that we evaluated clinical, laboratory and immunological parameters over time. There were 27 such patients in the main group.

Dynamics of subjective and objective symptoms in patients with diabetic foot syndrome.

As a result of the treatment, most patients of the main and comparative groups noted an improvement in well-being - a decrease and disappearance of pain in the area of the ulcerative defect, the disappearance of paresthesia, a decrease in the frequency of muscle cramps, an increase in endurance when walking. We did not find any significant differences in the dynamics of objective symptoms in the studied groups.

When comparing the time of relief of pain, normalization of body temperature and relief of acute phenomena in the group of patients in whom Superlymph was used, these indicators significantly (p<0.01) stopped faster than in the comparison group (Table 1)

Table 1

Comparative characteristics of the duration of the onset of relief of acute manifestations in patients with diabetic foot syndrome

Clinical signs	Main group (n=27)	Comparison group (n=34)
Relief of pain syndrome	4.4±1.0	5.2±0.9*
Normalization of the temperature reaction	4.3±0.8	5.0±0.9*
Relief of acute manifestations of inflammation	8.8±1	9.9±1.3*

* p<0,01 when comparing the trait in the main group of patients and in the comparison group.

Analysis of neurological status in groups of patients after treatment.

Immediately after the course of treatment, we examined the neurological status of both clinical groups: reflexes (Achilles and knee) and sensitivity (tactile, pain, temperature, vibration). The results of the study are presented in Table 2.

Table 2

Comparative assessment of changes in obituary status in patients of the observed groups before and after treatment (average over two legs)

Neurological status	Main group (n=27)		Comparison group (n=34)	
	Before treatment	After treatment	Before treatment	After treatment
Reflexes (points)	6.0±1.5	4.4±1.4*#	5.7±1.9	4.3±1.5*
Pain sensitivity (points)	3.3±0.8	1.7±0.7*##	3.2±0.9	2.9±0.8*
Tactile sensitivity (points)	3.4±0.8	2.4±0.8*#	2.9±1.2	2.1±1.1*
Threshold of vibration sensitivity on 1 finger (in conventional units)	2.5±1.1	3.8±1.0*##	2.4±1.2	2.8±1.1*
Temperature sensitivity (points)	4.7±0.6	3.4±0.8*#	4.4±0.7	3.4±0.9*

Conventional units are conventional units of vibration according to the tuning fork.

* p<0,05 - when comparing the trait before and after treatment in both groups.

p>0,05 - when comparing the trait of the main and comparative groups after treatment.

p<0,01 - when comparing the trait of the main and comparative groups after treatment.

As can be seen from Table 2, in the study of the neurological status in dynamics, a significant (p<0.05) improvement in almost all reflexes and types of sensitivity was noted in patients of both clinical groups. However, after treatment, pain sensitivity decreased, and vibration sensitivity increased significantly (p<0.01) in patients of the main group than in patients in the comparison group. Moreover, it should be noted that the threshold of vibra-

tion sensitivity before treatment in both groups was lower than the age norm (the lower limit of the norm of 60-70 years is 4.0 conventional units), and after treatment in the main group, the threshold of vibration sensitivity approached the norm of this age group - 3.8±1.0 conventional units, while in the comparison group, the vibration sensitivity index remained below the norm of - 2.8±1.1 conventional units.

Results of physical methods of examination of the feet after treatment.

Changes in the feet, such as dryness and atrophy of the skin, hyperkeratosis, deformity of the foot and toes, and thickening of the nail plates, which were detected during an external examination of the feet, persisted after the therapy in most patients of the observed groups, as they are persistent and irreversible changes. Oedema of the feet in patients of the main and comparative groups decreased significantly (p<0.05). However, in the main group, the swelling of the feet observed in 11 (40%) cases disappeared completely, while in the comparison group, oedema observed before treatment in 15 (44%) patients persisted after treatment in 8 (23.5%) patients (p<0.01).

Analysis of clinical and laboratory data after therapy.

In the analysis of clinical and laboratory signs of intoxication in both clinical groups after treatment, significant (p<0.05) differences in the level of leukocytes, stab neutrophils, and erythrocyte sedimentation rate were revealed (Table 3)

Table 3

Comparative dynamics of changes in intoxication indicators

Index	Main group (n=27)		Comparison group (n=34)	
	Before treatment	After treatment	Before treatment	After treatment
Body temperature (0C)	37.1±0.6	36.6±0.2*"	37.2±0.4	36.8±0.2*
Pulse (beats per minute)	82.8±5.2	73.4±5.5*"	83.1±5.1	75±5.3*
Leukocytes (thousands)	11.0±1.3	7.8±0.9*##	10.9±1.3	9.6±0.7**
Neutrophils (%)	70.5±3.6	61.3±2.5*#	70.6±3.4	65±3.1*
Erythrocyte sedimentation rate (mm/h)	36.7±5.2	11.5±2.3*"	38±9.5	18±3.7*

* p<0,01- when comparing the sign before and after treatment in each group.

** p<0,05 - when comparing the sign before and after treatment in each group.

" p>0,05 - when comparing the trait of the main and comparative groups after treatment.

# p<0,01 - when comparing the trait of the main and comparative groups after treatment.

p<0,05 - when comparing the trait of the main and comparative groups after treatment.

In the main group, there was a normalization of all parameters, in the comparison group, there was a normalization of the level of leukocytes and the erythrocyte sedimentation rate. Local cytokine therapy led to a decrease in the overall level of intoxication.

Analysis of microbial flora during therapy.

After the therapy, according to bacteriological studies, eradication of pathogens was achieved in 22 (81.5%) patients treated with Superlymph and in 18 (53%) patients in the comparison group. Data on the composition of the microflora of wound discharge exudate, before and after treatment, in the observed groups of patients are presented in Table 4.

Table 4.

Results of bacteriological studies in both clinical groups before and after treatment.

The causative agent of infection	Main group (n=27)		Comparison group (n=34)	
	Before treatment	After treatment	Before treatment	After treatment
Staphylococcus aureus	13 (48%)	1 (3.7%)**#	14 (41%)	4 (11.7%)**
Staphylococcus epidermis	11 (40.7%)	2 (7.4%)*#	11 (32%)	4 (11.7%)*
Enterococcus durans	5 (18.5%)	1 (3.7%)"#	4 (11.7%)	2 (5.9%)"
Enterococcus cloacae	2 (7.4%)	0"#	3 (8.8%)	0"
Peptococcus spp	5 (18.5%)	0*#	13 (38%)	2 (5.9%)**
Pseudomonas aeruginosa	8 (30%)	1 (3.7%)*#	13 (38%)	4 (11.7%)*
E. coli	1 (3.7%)	0"#	2 (5.8%)	0"

* p<0,05 - when comparing the sign before and after treatment in patients of both groups.

** p<0,01 - when comparing the sign before and after treatment in patients of both groups.

" p>0,05 - when comparing the sign before and after treatment in patients of both groups.

p>0,05 - when comparing the trait of the main and comparative groups after treatment.

As follows from the data given in the table, in the study of seeding from ulcerative defects after therapy, 4 types of microorganisms were identified in the study group in 5 (18.5%) patients versus 5 microorganisms in 16 (47%) patients in the comparison group. However, we did not observe significant differences in the quantitative value of each of the identified microorganisms after treatment in the main group and the comparison group.

When analyzing the X-ray examination of the feet and Doppler ultrasound of the arteries of the lower extremities, we did not reveal changes in the indicators of these studies after the course of treatment in any of the clinical groups, from which it follows that Superlymph,

being an immunomodulator, does not affect the remodelling of bone structures and stenotic changes in the arteries of the lower extremities in the neuro-ischemic form of diabetic foot syndrome.

The effect of Superlymph on the wound process.

For all patients of the observed groups before and after treatment, we performed wound planimetry and examined the local status: the area of the wound, the depth of the ulcer defect.

The area of the wound and the depth of the ulcerative defect after treatment were significantly ($p<0.05$) smaller in patients of the main group.

To analyze the effectiveness of local cytokine therapy with Superlymphomas, we studied the dynamics of the wound process in the patients we observed before and after the course of therapy. In patients in the comparison group, wound healing was slower compared to the study group (Table 5).

Table 5.

Dynamics of the wound process in the observed patients.

Criteria for the wound process (days)	Main group (n=27)	Comparison group (n=34)
Disappearance of oedema	7.5±1.6	9.8±2**
Terms of purification from necrotic masses	9.1±1.5	11.3±1.9*
The appearance of active granulation	6.0±1	9.2±1.5*
Epithelialization of the wound by 50%	10.9±1.6	12.6±1.7**
Average duration of treatment	20.5±1.5	26.2±3*

* p<0,01 - when comparing the trait of the main and comparative groups.

** p<0,05 - when comparing the trait of the main and comparative groups.

From the data given in Table 5, it can be seen that the dynamics of the course of the wound process in the main group were more intense. Apparently, under the influence of exogenous cytokines that make up Superlymph, there is a change in the intrinsic cytokine background of tissues, a local cytokine cascade is launched, followed by an increase in the proliferation of T and B lymphocytes, their migration from the lymphatic system into the blood and the focus of inflammation, as well as activation of migration and fixation of macrophages in the focus of inflammation and an increase in their phagocytic activity [5].

The complex of cytokines included in Superlymph stimulates collagen synthesis, a proliferation of fibroblasts, endothelial cells, and nerve formations. All of the above determines the local and less pronounced nature of the inflammatory response [26].

8-10 minutes are enough to connect cytokines that are part of Superlymph with receptors of target cells, thus, cytokines and growth factors of the drug do not have time to be inactivated by protein kinases of wound discharge exudate [34].

All of these properties of Superlymph allowed us to achieve faster positive dynamics of the wound process.

Evaluation of cytokine levels (IL-8 and TGF-β) in patients with diabetic foot syndrome after treatment. In the group of patients receiving Superlymph, there was a significant decrease in the pro-inflammatory cytokine IL-8 and a significant increase in the anti-inflammatory cytokine TGF-β. According to the correlation analysis in the main group, a negative correlation relationship ($r=-0.81$, $p<0.05$) between the levels of IL-8 and TGF-β after treatment was revealed. This correlation was not found in the comparison group.

When correlations were detected between the level of cytokines studied and the levels of leukocytes, neutrophils, and erythrocyte sedimentation rate after treatment, correlations were detected only in patients of the main group. A positive relationship was found between the level of IL-8 and the level of leukocytosis: $g=0.8$, $p < 0.05$. and also revealed a negative correlation between the level of TGF-β the levels of leukocytes, neutrophils and erythrocyte sedimentation rate: $g=-0.76$, $p<0.05$ and $g=-0.47$, $p<0.05$ and $g=0.83$, $p<0.05$, respectively.

Evaluation of the effectiveness of treatment of patients with diabetic foot syndrome based on the results of the data obtained.

When evaluating the effectiveness of treatment, we noted good results, satisfactory and unsatisfactory results. With the traditional method of treatment of patients with diabetic foot syndrome, a good treatment result can be achieved only in 38.2% of patients, at the same time, as with the use of Superlymph, this effect can be obtained in 71% of patients. With the use of Superlymph, it was possible to reduce by 2.3 times the number of patients with an unsatisfactory treatment results compared to traditional treatment.

CONCLUSION

In patients with diabetic foot syndrome, changes in the local cytokine status in the exudate of the wound discharge are presented in the form of an increase in the pro-inflammatory cytokine IL-8 and a decrease in the anti-inflammatory cytokine TGF-β. As a result of the study, positive correlations were established between the duration of diabetes mellitus, the level of glycated haemoglobin and the initial level of IL-8 and negative correlations between the duration of diabetes mellitus, glycated haemoglobin and the initial level of

TGF-β. At the same time, the analysis of data on the content of the studied cytokines in the exudate of wound discharge did not reveal statistically significant differences in cytokine levels in neuropathic and neuro-ischemic forms of diabetic foot syndrome.

Superlymphoma topical therapy helps to increase the level of anti-inflammatory (TGF-β) and reduce the level of pro-inflammatory (IL-8) cytokines in the exudate of wound discharge in patients with diabetic foot syndrome. In this connection, after treatment in the group of patients receiving Superlymph, a negative correlation between the levels of IL-8 and TGF-β was revealed. This contributes to more rapid normalization of intoxication parameters, intensive positive dynamics of the wound process, reduces the length of hospital stay from an average of 26 to 20 days, and contributes to the eradication of bacterial flora from the focus of inflammation.

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DIABETIK OYOQ SINDROMINING ÜLSERATIV-NEKROTIK JAROXATNI DAVOLASHDA YANGI YONDASHUVLAR

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ABSTRAKT

Dolzarbligi. So'nggi yillarda qandli diabet bilan og'ruvchi bemorlarda surunkali yaralarni davolashda sitokoknlar va turli o'sish omillaridan foydalanish katta qiziqish uyg'otmoqda.

Material va usullar. Diabetik oyoq sindromi bilan og'rigan 2-tip qandli diabet bilan og'rigan 72 nafar bemorni davolash natijalari keltirilgan bo'lib, ular ikki guruhdan iborat: asosiy guruh (diabetik oyoq sindromini standart davolash bilan bir qatorda, umumiy qabul qilingan sxemaga ko'ra immunomodulyator Superlimfaning eritmasi bilan mahalliy dasturlarni o'tkazgan 38 nafar bemor) va solishtirish guruhi (ushbu patologiya uchun an'anaviy davolashni qo'llagan 34 nafar bemor). Klinik moslamalarda mavjud bo'lgan klinik, laboratoriya va instrumental tadqiqot usullari qo'llanildi.

Natija va xulosalar. Yallig'lanishga qarshi kurashning pasayishi va yallig'lanish tarafdori sitosinlarning ko'payishi ko'rinishidagi mahalliy sitosin holatining o'zgarishi diabetik oyoq sindromi bilan og'rishga moyil bemorlarga xosdir. Yaralar chiqishi ekssudati sitozinlarining darajasi qandli diabetning davomiyligiga, glikatlangan gemoglobin va leykotioz darajasiga bog'liq bo'lib, diabetik oyoq sindromi shakliga bog'liq emas. Diabetik oyoq sindromi bilan og'rigan bemorlarning kompleks terapiyasida Superlimphdan foydalanish immunitet holatini normallashtirishga hissa qo'shadi, bu esa o'z navbatida diabetik oyoq sindromida ulcerativ oyoq nuqsonlarini samarali sog'lomlashtirishni ta'minlaydi.

Tayanch iboralar: 2-tip qandli diabet, diabetik oyoq sindromi, sitokinlar, sitokin terapiyasi

НОВЫЕ ПОДХОДЫ К ЛЕЧЕНИЮ ЯЗВЕННО-НЕКРОТИЧЕСКИХ ПОРАЖЕНИЙ СИНДРОМА ДИАБЕТИЧЕСКОЙ СТОПЫ

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АБСТРАКТ

Актуальность. Большой интерес в последние годы вызывает использование цитокинов и различных факторов роста в лечении хронических ран у больных сахарным диабетом.

Материал и методы. Представлены результаты лечения 72 больных сахарным диабетом 2 типа с синдромом диабетической стопы, составившие две группы: основную и группу сравнения. Использовались клинико-лабораторные и инструментальные методы исследования, доступные в клинических условиях.

Результаты и выводы. Изменение локального цитокинового статуса в виде снижения противовоспалительных и повышения провоспалительных цитокинов характерно для больных с синдромом диабетической стопы. Уровни цитокинов экссудата раневого отделяемого зависят от длительности сахарного диабета, уровня гликированного гемоглобина и лейкоцитоза и не зависят от формы синдрома диабетической стопы. Применение Суперлимфа в комплексной терапии больных с синдромом диабетической стопы способствует нормализации иммунного статуса, что в свою очередь обеспечивает эффективное заживление язвенных дефектов стоп при синдроме диабетической стопы.

Ключевые слова: Сахарный диабет 2 типа, синдром диабетической стопы, цитокины, цитокиновая терапия