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# PATHOGENETIC AND CLINICAL FEATURES OF THE COURSE OF PURULENT-NECROTIC COMPLICATIONS OF DIABETIC FOOT SYNDROME

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**Abstract:** today there are more than 150 million people with diabetes mellitus (DM) in the world. The main role in the progression of late complications of diabetes belongs to chronic hyperglycemia and the lack of compensation for the latter. The incidence of diabetic foot syndrome (DFS) in the last years of the 20th century. increased more than 5 times, however, the pathogenesis of its development and the variety of variants of the clinical course of destructive processes in the lower extremities are still not fully understood. In addition, a pronounced effect from treatment of this category of patients is not always observed, and in the available literature there is no description of uniform approaches to diagnosis and treatment, or understanding of the etiopathogenesis of the development of purulent-necrotic complications of diabetic foot syndrome. . It can be assumed that the development of vascular complications of diabetes requires the presence of both external (chronic hyperglycemia) and internal (genetic) factors.

**Key words:** diabetic foot, complications, microangiopathy, macroangiopathy, neuropathy, gene polymorphism, lymphovenous lesions, immunity, mycoses.

# DIABETIK OYOQ SINDROMINING YIRINGLI-NEKROTIK ASORATLARINING PATOGENETIK VA KLINIK XUSUSIYATLARI

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**Xulosa:** bugungi kunda dunyoda 150 milliondan ortiq diabet kasalligi (DM) mavjud. Qandli diabetning kech asoratlarining rivojlanishida asosiy rol surunkali giperglikemiya. 20-asrning so'nggi yillarida diabetik oyoq sindromi (DFS) bilan kasallanish. 5 baravardan ko'proq oshdi, ammo uning rivojlanish patogenezi va

oyoqlarni distal soxasi ishemiyasi halokatli jarayonlarning klinik kechishining turli xil variantlari hali ham to'liq tushunilmagan. Bundan tashqari, ushbu toifadagi bemorlarni davolashning aniq ta'siri har doim ham kuzatilmaydi va mavjud adabiyotlarda diagnostika va davolashning yagona yondashuvlari yoki diabetik yiringli-nekrotik asoratlar rivojlanishining etiopatogenezini tushunish tavsifi yo'q. oyoq sindromi. Qandli diabetning qon tomir asoratlarining rivojlanishi tashqi (surunkali giperglikemiya) va ichki (genetik) omillarning mavjudligini talab qiladi deb taxmin qilish mumkin.

**Kalit so'zlar:** diabetik oyoq, asoratlar, mikroangiopatiya, makroangiopatiya, neyropatiya, gen polimorfizmi, limfovenoz kasallik, immunitet, mikozlar.

# ПАТОГЕНЕТИЧЕСКИЕ И КЛИНИЧЕСКИЕ ОСОБЕННОСТИТЕЧЕНИЯ ГНОЙНО-НЕКРОТИЧЕСКИХ ОСЛОЖНЕНИЙ СИНДРОМА ДИАБЕТИЧЕСКОЙ СТОПЫ

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**Аннотация:** сегодня в мире насчитывается более 150 миллионов больных сахарным диабетом (СД). Основная роль в прогрессировании поздних осложнений СД принадлежит хронической гипергликемии и отсутствию компенсации последней. Заболеваемость синдромом диабетической стопы (СДС) в последние годы 20 века. увеличилась более чем в 5 раз, однако патогенез ее развития и многообразие вариантов клинического течения деструктивных процессов в нижних конечностях до сих пор до конца не изучены. Кроме того, не всегда наблюдается выраженный эффект от лечения данной категории больных, а в доступной литературе нет описания единых подходов к диагностике и лечению, понимания этиопатогенеза развития гнойно-некротических осложнений синдрома диабетической стопы. . Можно предположить, что для развития сосудистых осложнений СД необходимо наличие как внешних (хроническая гипергликемия), так и внутренних (генетических) факторов.

**Ключевые слова**: диабетическая стопа, осложне- ния, микроангиопатия, макроангиопатия, нейропа- тия, полиморфизм генов, лимфовенозные пораже- ния, иммунитет, микозы.

**Relevance.** According to WHO, today there are more than 150 million patients with diabetes mellitus (DM) in the world. The main role in the progression of late complications of diabetes belongs to chronic hyperglycemia and the lack of compensation for the latter. The incidence of diabetic foot syndrome (DFS) in the last years of the 20th century. increased more than 5 times, but the pathogenesis of its development and the variety of variants of the clinical course of destructive

processes in the lower extremities is still not fully understood. In addition, there is not always a pronounced effect from treatment of this category of patients, and in the available literature there is no description of uniform approaches to diagnosis and treatment, understanding the etiopathogenesis of the development of purulent-necrotic complications of diabetic foot syndrome. It can be assumed that the development of vascular complications of diabetes requires the presence of both external (chronic hyperglycemia) and internal (genetic) factors [37].

Taking into account the likelihood of a genetic predisposition to the formation and course of destructive processes in the lower extremities, we studied the frequency distribution of alleles of genetic variants (mutations, polymorphisms) of "candidate" genes associated with the development of cardiovascular pathology: C677T of the MTHFR gene, E2/E3/ E4 of the ApoE gene, I/D of the ACE gene. The studied molecular genetic markers may be associated with risk factors for the development of cardiovascular pathology and participate in the formation of angiopathy of the lower extremities. The C677T mutation of the MTHFR gene is associated with hyperhomocysteinemia, which plays a significant role in damage to the vascular endothelium and provokes a tendency to thrombosis. The well-studied I/D polymorphism of the ACE gene, in turn, is associated with the development of arterial hypertension and is a leading risk factor for the development of coronary heart disease. More rare alleles of the ApoE gene (E4/E2) are associated with changes in the rate of apolipoprotein catabolism, which can be associated with a predisposition to the development of atherosclerosis [28].

It is likely that a certain number of patients have "candidate" genes that, under the influence of external factors, initiate the development of vascular complications [12]. Results of a large number of scientific studies confirm the connection between dyslipidemia and atherosclerotic vascular lesions [22]. Diabetic angiopathy, according to various sources, is detected in 70–90% of patients [2, 9, 11, 18].

D.F. Erdmanis [21] indicates that diabetic macroangiopathy is an independent process, and not early atherosclerosis (based on morphological data). Vascular lesions manifest themselves in the form of: 1) the presence of fatty plaques on the intima; 2) Mecklenberg calcific sclerosis; 3) diffuse intimal fibrosis.

Diabetic macroangiopathy is characterized by insufficient development of collaterals and distal level of vascular damage. Vascular occlusions in diabetes are multisegmental, bilateral and diffuse in nature, in contrast to patients without diabetes. Along with lesions of large and medium-sized vessels, large changes occur in arterioles with a diameter of 0.3 mm or less. They develop proliferation and hyalinization of the intima, leading to narrowing of the lumen, which contributes to the development of ischemia of peripheral tissues [13].

Today, there is numerous data on the connection of polymorphic genes of lipid metabolism with the regulation of various parts of the pathogenesis of atherosclerosis and associated diseases, but there is no information about the

influence of the latter on the development and course of diabetic angiopathy and its role in the pathogenesis of DFS [25, 32 ].

Diabetic microangiopathy is manifested by changes in the capillary bed. In patients suffering from diabetes, thickening of the basement membranes of the capillaries, their tortuosity, blockage or dilatation of the lumen of the vessel is detected. Vital microscopy of the capillary bed reveals expansion of capillaries in the distal phalanges of the fingers, and extensive angiography reveals avascularized zones and microaneurysmal dilatations in the area of the digital arterial network [27]. These disorders include increased permeability of vascular walls, impaired autoregulatory functions, impaired reactivity, but in themselves are not the cause of the appearance of
foot ulcer [36].

The nature of changes in arteries, capillaries, nerve trunks and the osseous-ligamentous apparatus in diabetes mellitus is widely covered in the literature, however, the systemic nature of changes in type II diabetes mellitus and the characteristic purulent-necrotic lesions of the lower extremities suggest the presence of pathological changes in absolutely all anatomical structures and systems for SDS. In other words, one might think that with DFS, the venous and lymphatic systems directly connected to the arterial system cannot remain intact.

Thus, patients suffering from DFS, as well as patients with diseases of the veins of the lower extremities, with a clinically manifested disease, are faced with the formation of trophic ulcers of the lower extremities. Ulcers in diabetes and venous pathology have a number of different features and similar manifestations [5]. However, there are often cases of persons with VDS in whom varicose changes in the veins of the lower extremities are slightly expressed, while the ulcers are of a typical venous nature [14]. It would probably be appropriate in this case to assume a special nature of venous damage in DFS, closely related to a violation of the microcirculatory link of pathogenesis.

In the domestic and world literature there is little data on studies of the venous and lymphatic system in DFS; accordingly, objective data on the problems under consideration seem unsystematized, often being random observations in the main line of research that is not related to the issue being covered. This fact is puzzling, since most specialists involved in the study and treatment of diabetes mellitus regularly note the widespread prevalence in patients with type II diabetes mellitus of erysipelas, chronic venous insufficiency and mycotic lesions of the feet - those pathological conditions that are widely interconnected. discussed and practically obvious [10]. However, there is no data on the correlation of these diseases with purulent-necrotic lesions in DFS.

According to R. Mani et al. [29] in 85% of patients with diabetes Type II there are signs of pathological changes in the veins of the lower extremities. This fact was revealed when measuring the blood filling of the venous vessels of the lower limb according to the results of laser Doppler flowmetry [29]. It can be assumed that

accelerated blood filling of the leg veins in patients with diabetes is a consequence of venous stagnation of blood, which, in turn, is macroscopically manifested by dilation of the veins. Accordingly, it is necessary to identify factors predisposing to venous stasis that are characteristic specifically for patients with type II diabetes with purulent-necrotic complications of vascular dysplasia.

First of all, this is a violation of blood flow from the arterial system. Disturbances immediately develop in the mechanisms that ensure normal circulation of venous blood in the lower extremities. This, naturally, is macroangiopathy, which causes a violation of adequate blood flow through the arterial system of the limb, as well as a deterioration in the pumping function of the right parts of the heart, which, again, is easily explained in people with increased body weight and atherosclerosis of the coronary arteries. The presence of microangiopathy, coupled with changes in the rheological properties of blood, ultimately manifests itself as a limitation in the volume of capillary circulation. Excessive blood pressure in the precapillary bed stimulates the opening of a large number of arteriovenous shunts and active discharge of blood into the veins.

In addition, hemodynamic disturbances are actively influenced by changes in the functioning of the blood coagulation system. The biochemical mechanisms of these processes are associated with an increase in thromboxane synthesis and a decrease in prostacyclin production under the influence of hyperglycemia, and they are quite well studied [9]. Obviously, this is the number one problem for the microvasculature, where in conditions

When blood flow speed decreases, erythrocyte sludge turns into blood clots. However, in veins overloaded with excess blood volume under conditions of obstructed outflow, blood clots also actively form [33].

To date, the role of the lymphatic system in the pathogenesis of DFS remains unclear. There are very scarce, sometimes contradictory data, mainly from Novosibirsk scientists [14]. According to some authors, there is an increase in lymphatic drainage from the affected limb; according to others, on the contrary, there is a block or a sharp decrease in lymphatic drainage in the affected limb. When performing rheolymphovasography in patients with DFS, disturbances in the venous and lymphatic outflow of the limb are noted, expressed in a decrease in the speed and volume of outflowing lymph and peripheral venous blood [15, 16].

For the first time, the influence of neuropathy on the formation of foot ulcers and the development of gangrene began to be studied only in the middle of the twentieth century. [thirty]. According to various authors, diabetic neuropathy is present in 12–90% of patients. Such discrepancies are explained by the lack of uniform diagnostic criteria and differences in methods for identifying diabetic neuropathy. The leading role in identifying early signs of disorders in the peripheral nervous system is given to electrophysiological methods (electromyography). Research data reveal a slowdown in the conduction of excitation along the nerves in

12% of patients [31]. Signs of neuropathy correlate with the level of compensation of carbohydrate metabolism and long-term illness in 10% of patients [20].

As a cause of DFS, including gangrene, peripheral sensitivity plays an important role and autonomic neuropathy. Patients with the neuropathic form of DDS make up 60–70% of all patients with DDS. Somatic, long-term sensorimotor neuropathy leads to deformation of the foot, caused by an imbalance between the flexors and extensors, with a predominance of tension in the extensor tendons and protrusion of the heads of the metatarsal bones. As a result, areas of hyperkeratosis are formed that experience excessive stress, inflammatory autolysis of soft tissues develops, and ulcers form [21, 38].

The consequence of autonomic neuropathy is calcification of the tunica media of the artery (Mecklenberg sclerosis), leading to loss of elasticity of the vascular wall, resulting in blood discharge through arteriovenous shunts and a decrease in actual blood flow in the tissues [27]. The neuropathic process causes atrophy of the intrinsic muscles of the foot with subsequent deformation. A deformed foot, due to compression by shoes, as well as improper gait, leads to the formation of calluses, and at points of greatest stress - to trophic ulcers. The skin in the zone of constant friction is largely infected, the intensity of microcirculatory blood flow in it is reduced, and microtraumas lead to the formation of deep abscesses and phlegmons. Clinically, neuropathy manifests itself in the form of chronic recurrent trophic ulcers, painless osteomyelitis, and gangrene. Dry gangrene with a clear demarcation line develops more often [17, 23]. Currently, for the differential diagnosis of denervation changes in muscles against the background of DFS, chronaximetric electrodiagnostics are performed [17].

In non-insulin-dependent diabetes there is an increase
reduction in the absolute amount of immunoglobulins G,
decreased number of mature T lymphocytes, normal composition of mononuclear cells in peripheral blood in patients with different durations of the disease [7]. Immunity changes similar to those in insulin-dependent diabetes are also detected: an increase in the absolute amount of immunoglobulins of classes M and A, the appearance of activated B-lymphocytes (CD22), and the occurrence of an imbalance between T- and B-cells. The ratio of T-suppressors (CD8) to T-helpers (CD4) is reduced by helpers, and blast transformation of T-lymphocytes and phagocytes is suppressed [1]. A decrease in IgG content leads to the progression of angiopathy. With the development of diabetic gangrene, the absolute number of T-lymphocytes continues to decrease, and the number of B-lymphocytes of all populations also decreases, except CD22, the number of which increases. There are no violations in the balance of factions. Thus, the cellular component of immunity is depressed, and the number of immunoglobulins increases: the number of IgA increases by 1.5 times, the number of IgM and IgG increases insignificantly. The ratio of CD4 to the number of immunoglobulins (suppression index) is below normal [4]. With the generalization of the purulent-necrotic process (sepsis), the severity of all immune

changes increases, and in the terminal stage, all immune indicators are suppressed [3].

For a more complete assessment of the condition of nonspecific

The body's resistance is determined by the leukocyte index of intoxication. The point of view according to which an increase in the CD4/CD8 index is a specific marker of the presence of a purulent-necrotic process in diabetic foot syndrome has been confirmed: if in patients with stage III DFS this index was 1.8, then in patients with stage V - already 2.4. In general, a violation of the immunological reactivity of the body is detected in all patients with DFS [8].

In the wound contents of patients with a purulent-necrotic process during DFS, staphylococci are most often found in monoculture - in 58% and in associations - in 45%. The dominant one is St. aureus - 86%, less often St. heamolyticus - 7%, St. epidermietus - 5%, St. xylosus - 2%. Gram-negative flora was isolated only in associations in 37% of patients and was represented by a group of enterobacteria, which were: Proteus - 12%, Klebsiella - 9%, Enterobacter - 7%, Citrobacter - 3%, Escherichia - 6%. In addition, there were Cl. perfringens, Ps. aeruginosa, Bacteroiodes sp., Candida sp. In addition, the microbial landscape is different in the depth of the wound and on its surface. The leading role in the underlying tissue layers is played by gram-negative flora and fungal bacteria [6]. According to the currently available literature data, it seems difficult to determine the significance of mycotic lesions as a risk factor for complications of DFS. The frequency of mycotic lesions in patients with DFS, as in the general population, varies widely. E.I. Zoloeva et al. [10] provide the following data: onychomycosis of the feet occurs in 1/3 of patients with diabetes, of which

44.3% - patients with mycotic lesions of the feet

and 33.6% - with vesiculoexudative mycosis, in whom the examination revealed impaired glucose tolerance. At the same time, E.M. Staroselsky [20], based on his own research, showed that the frequency of mycoses in patients with DFS ranges from 1 to 17 per 100 examined, while the mycotic lesion is often superficial, non-invasive, and does not which is a leading factor in the formation of the entrance gate for infection during purulent-necrotic complications of DFS. According to V. Elewski [24] in the USA, fungal infections

On average, 2–3% of the population suffer from foot problems. He indicates a number of risk factors for the development of mycoses: diabetes, immunodeficiency states, ketoacidosis and hyperglycemia [24, 26].

Currently, studies by a number of authors have revealed a correlation between the duration of the disease, the severity of diabetes and the number of foci of fungal infection on the affected limb. In 2000, J. Ribes et al. [34], describing fungi of the Zygomycetes class that are pathogenic for humans, give the following clinical picture of lesions on the skin of the feet: mycosis can be both superficial and deep, affecting all layers of the skin; it is also possible to develop myositis and fasciitis with the formation of abscesses or necrosis of soft tissues of varying degrees of severity.

The microbial landscape of the lesion is polymorphic, and the clinical course is characterized by rapid aggressive development, and the pathogenic flora turns out to be resistant to drug treatment. In patients with severe decompensated diabetes, as shown by W. Sheldon and H. Bauer [35], fungal dissemination develops, occurring predominantly through the hematogenous route. This is actively promoted by hyperglycemia and ketoacidosis, which inhibit the phagocytic activity of macrophages and their ability to perform peroxide-cytotoxic effects in body tissues [35]. Severe forms of neuropathy of the lower extremities in DFS increase the risk of developing purulent-necrotic complications with concomitant onychomycosis. Altered nail plates can contribute to traumatization of surrounding soft tissues and lead to the formation of erosions nail bed, which, given the proximity of the underlying bone, can cause the development of osteomyelitis. In the neuroischemic form of DDS, isolated damage to the nails is more common, while in patients with the neuropathic form of DDS, both damage to the skin of the feet and deformation of the nail plates occur [10].

Polymycosis is observed in 44.5% of patients with diabetes, and in 1/3 of patients generalization of the infectious process is noted. A relationship was revealed between the speed of regional blood flow and the qualitative parameters of the microflora of the skin of the feet. In a number of fungal invasions, when the process is generalized, mortality can reach 96–100% [34].

In patients with mycoses of the feet, secondary bacterial lesions occur in 48.7% of cases. As a result of the production of antibiotic-like substances by fungi, the pyococcal flora acquires increased resistance to antibacterial drugs, as a result of which patients with foot mycoses become potential sources of the spread of not only fungal, but also bacterial pathology. In this group of patients, 20–25% experience the development of severe forms of erysipelas and a more severe course of other types of purulent-necrotic processes [10].

**Summary**: Thus, the problem remains unresolved, which requires continued molecular genetic and morphological studies for a more detailed and complete understanding of the state of all vascular structures: arteries, veins and lymphatic vessels of the lower extremities in patients with purulent-necrotic lesions in DFS, which is necessary for understanding the mechanisms of pathogenesis.

We also consider it advisable to continue research aimed at establishing a cause-and-effect relationship between pathological changes in the arterial, venous, lymphatic and nervous systems and the influence of their interaction on the occurrence and development of destructive processes in the tissues of the foot. It is necessary to resolve the issue of the nature and volume of immunocorrective therapy in patients with DFS, as well as the timing of its implementation, since immune disorders are specific and are not observed at all levels.

In our opinion, it is mandatory to conduct research that will accurately establish the role of mycotic lesions of the extremities in the development and

course of purulent-necrotic processes and the pathogenesis of DFS, which will have a significant impact on the choice and use of antibacterial and antimycotic therapy.

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