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Review Article

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Pathogenetic Aspects of the Development of Diabetic Foot Syndrome

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ABSTRACT

At present, much has been achieved in the field of treatment of diabetic foot syndrome, and multidisciplinary treatment approaches have been developed. However, despite all the achievements, the number of leg amputations in diabetes is growing. Every hour in the world, 55 patients with diabetes lose their lower limbs, and in economically developed countries, it varies from 13.7 to 32.3 per 100 100,000 population, which in turn is accompanied by a high mortality rate, costs for treatment and rehabilitation. Studies have established that the course of the wound process is accompanied by a dynamic change of various biological reactions of the body, subject to the influence of many endogenous and exogenous factors that determine smooth wound healing or the development of various complications. One of the urgent problems today, which requires specialists to solve their solution, is developing immunopathogenetic mechanisms to increase the effectiveness of surgical and therapeutic measures in patients with diabetes mellitus complicated by diabetic foot syndrome, which occurs among the population of developed countries. This review article is devoted to the pathogenetic aspects of the development of diabetic foot syndrome.

Keywords: *diabetes mellitus, diabetic foot syndrome, pathogenesis*

In the last decade, the attention of specialists, including immunologists involved in the diagnosis and treatment of patients with diabetes mellitus, has been closely paid to diabetic foot syndrome. This is due to the growth of this complication, on the one hand, and dissatisfaction with the results of treatment, on the other hand [1].

Despite certain successes in the treatment and prevention of diabetic foot syndrome, still 40-60% of all non-traumatic amputations of the lower extremities are performed in patients with diabetes mellitus. In some regions, this figure reaches 70-90% [2].

The annual rate of "major" amputations in industrialised countries ranges from 0.06 to 3.86 per 10,000 patients with diabetes.

In the global consideration of this problem, it has been established that 55 amputations are performed every hour for this pathology. Despite the colossal mater-

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ial costs, the mortality rate from purulent-necrotic complications of diabetic foot syndrome ranges from 6 to 20%. Mortality in patients with diabetes mellitus after "major" amputations ranges from 40 to 57% over the next three years and from 50 to 75% over the next five years. Five years in 50-66% of patients [3].

The above epidemiological indicators determine the high social and economic significance of the problem of diabetic foot syndrome. This leads to the close attention of various state and public services both in our country and abroad, especially since, in several countries, it has already been proven in practice to prevent 50% of amputations [4].

The International Consensus on the Diabetic Foot, as amended, is considered to be the fundamental document for the diagnosis and treatment of diabetic foot syndrome [International Consensus on the Diabetic Foot, 2007]. According to this document, diabetic foot syndrome is an infection, ulcer and/or destruction of deep tissues associated with neurological disorders and a decrease in the main blood flow in the arteries of the lower extremities of varying severity.

In the literature, diabetic foot syndrome is defined as a pathological condition of the feet of a patient with diabetes mellitus, which occurs against the background of damage to peripheral nerves, blood vessels, skin and soft tissues, bones and joints and is manifested by acute and chronic ulcers, osteoarticular lesions, and purulent-necrotic processes [5].

The classic pathogenetic triad of diabetic foot syndrome includes ischemia, neuropathy, and infection. All these factors can cause the development of diabetic foot syndrome both independently and in combination with other causes. Based on the predominance of one or another factor, three forms of diabetic foot syndrome are distinguished: neuropathic (60-75%), neuroischemic (20-30%) and ischemic (5-10%) [International Consensus on the Diabetic Foot, 2007].

Prolonged hyperglycemia and transient ketosis lead to serious impairments in antimicrobial protection with primary damage to specific and non-specific factors of the immune system of patients.

This is manifested in a decrease in the activity of phagocytes, including phagocyte chemotaxis, the bactericidal function of non-specific resistance factors, and a decrease in the activity of immunocompetent cells in the body of patients [6].

Various pathogenic and opportunistic microorganisms in diabetic foot syndrome are a limb-threatening condition that causes emergency amputations in 25-50% of cases and a high postoperative mortality rate reaching 10-15% [7].

By changing the chemist and osmolarity of the internal environment, hyperglycemia leads to structural pathology of the vascular and nervous systems. This is especially true for the immune system, a decrease in the activity of which leads to the development of secondary immunodeficiency. Weak immune protection leads to high contamination of the wound with pathogens [8].

Damage to blood vessels in diabetes occurs in the form of microangiopathy when the microcirculation system is damaged with the development of an occlusive-stenotic process in large and medium-sized arteries. Diabetic microangiopathy is multi-component.

Hyperglycemia alters the metabolism of mucopolysaccharides and induces the formation of low-density lipoproteins. Glycoproteins accumulate in the basement membrane of the foot arterioles; the membrane thickens, which prevents transcapillary diffusion of oxygen. Damage to the capillary bed in the form of productive vasculitis causes collagenopathy and deposition of circulating immune complexes in the walls of blood vessels, i.e. an antigen-antibody complex that causes an immune response [9].

Impaired lipid metabolism as a result of hyperglycemia leads to early atherosclerotic lesions of the main arteries of the lower extremities [10]. Tissue ischemia is mainly caused by macroangiopathy. Early atherosclerosis, leading to stenosis and occlusion of the arteries, the development of ischemic syndrome, is not observed in all patients with diabetic foot syndrome. This complication occurs in 17.8-46.4% of patients [11]. Macroangiopathy in diabetes is multi-segmental. It most often affects the tibial vessels, dorsal, plantar arteries and arterioles of the foot and involves collaterals located near the occlusion site.

Lesions of large arteries below the knee joint lead to ischemic complications much more often than microangiopathy. However, there are reasoned opinions of the opposite nature.

In addition to early atherosclerosis, diabetes mellitus, as previously mentioned, is characterised by arterial mediocalcinosis or Menkeberg's sclerosis, in which fibrosis develops in the middle lining of the arteries of the lower leg and foot and calcium salts are deposited. This causes intimal hypertrophy with stable, non-obliterating narrowing of the arterial lumen.

Signs of critical ischemia of the lower extremities depend on the level of narrowing or occlusion of the artery and the degree of development of collateral circu-

lation, which is of fundamental importance in the development of purulent-necrotic processes in patients with diabetes mellitus.

It is worth mentioning the property of endotheliocytes of blood vessels to remain viable in conditions of critical ischemia, including that developed as a result of diabetic angiopathy. This phenomenon, studied by Zemlyanoy A.B. [2003], is of great scientific and applied importance. After the elimination of critical ischemia of the lower extremities, achieved by treatment, microvessels are restored due to the proliferation of endotheliocytes. This process, called neocapillarogenesis, contributes to the preservation of the limb.

There are other causes of tissue ischemia associated with diabetes. These include impaired oxygen transport due to its increased affinity for glucose-derived haemoglobin. Impaired oxygen transport and hemorology are exacerbated by acute purulent inflammation, which leads to an even greater deterioration of microcirculation against the background of diabetic angiopathy [8].

It is known that macroangiopathy leading to decompensated ischemia is complicated by the development of wet gangrene of the extremity. Wet gangrene always develops as a result of the addition of anaerobic and putrefactive infections [12]. Polymorphic, opportunistic bacterial flora is sown out of the wounds of patients with diabetes mellitus. In 36.8-56.8% of cases, non-clostridial anaerobes and other causative agents of putrefactive infection are found. Its pathogenicity and virulence allow us to talk about nosocomial infection [13].

The main microorganisms that first colonise and then infect damaged skin are Staphylococcus aureus and β-hemolytic streptococci. They are secreted in new superficial foot ulcers in patients who are not treated with antibiotics.

In chronic recurrent ulcers treated with antibiotics, polymicrobial flora is already isolated, including gram-positive cocci, Enterobacteriaceae, and obligate anaerobes. In patients with a long-term non-healing wound against the background of antibiotic treatment, gram-positive costs (including methicillin, resistant Staphylococcus aureus, coagulase-negative staphylococci, enterococci), Enterobacteriaceae, non-fermenting pathogens (Pseudomonas aeruginosa, Pseudomonas aeruginosa, acinetobacter) and anaerobes. It should be noted that the frequency of isolation of multidrug-resistant pathogens is directly related to the frequency and duration of antimicrobial use [14].

Repeated hospitalisations, long-term therapy with broad-spectrum antibiotics, and surgical treatment, which are predisposing factors for infection of foot wounds with multiresistant microorganisms, significantly worsen the prognosis of treatment [15].

In severe purulent-necrotic lesions in patients with diabetes mellitus, mixed aerobic-anaerobic microflora is more often isolated (87.7% of cases), only aerobic – in 12.3% [16].

It has been established that patients with diabetic foot syndrome have disorders of the immune system, expressed in a weakened immune response, a decrease in phagocyte activity, the production of specific antibodies, and the development of severe secondary immunodeficiency [17].

It has been revealed that along with a decrease in immunological resistance, the activity of fibroblasts is inhibited, and the regeneration period is lengthened. The exudative phase of inflammation is lengthened and becomes excessive. Tissue ischemia also serves as a brake on regeneration. When TsrO2 decreases to 30 mm Hg, regeneration slows down, and below 25 mm Hg becomes impossible [18].

The variety of clinical manifestations of diabetic foot syndrome is directly related to the predominance of one or another pathological process underlying the disease. In some cases, it is possible to note only signs of neuropathy combined with atrophic or degenerative-dystrophic lesions of the foot skeleton. In such patients, there is no clinical ischemia of the lower extremities, which gives the right to attribute them to the neuropathic form of diabetic foot syndrome. In other patients, there are no signs of neuropathy, but disorders of the main circulation are manifested, up to severe ischemia and even necrosis of part of the foot.

Patients with such a clinical picture are unhesitatingly referred to the ischemic form of the disease, 15-40% of them sooner or later develop ulcerative-necrotic complications that require surgical treatment and often lead to amputations. Among all non-traumatic amputations of the lower extremities, up to 60% occur in patients with diabetes mellitus. With the development of critical limb ischemia, these figures acquire rather sad statistics [19].

The result of amputation is usually evaluated only from the point of view of stump healing and mortality. Thus, after amputations at the hip level, 10-40% of operated patients die, and 5-20% at the level of the lower leg. Within three years after high amputations at the hip level, from 40 to 57% of patients die, and by five years, 50-75% of patients die [20].

In the next five years, amputees at the hip level develop destructive complications from the single collateral limb, which in 50-67% of cases also ends in its amputation.

Survivors often cannot work and take care of themselves and cannot leave the house even with the help of strangers.

The basis of modern principles for choosing the level of amputation is the preservation of the largest possible part of the lower limb, provided that the stump heals and is suitable for prosthetics: the lower the level of amputation, the lower the degree of disability of the patient and the more often the ability to work is preserved. With longer stumps, the curvature of the spine is less pronounced, which also affects the general condition of the patient. When the knee joint is preserved, the collateral limb functions better and with less load, which is important, given the almost always bilateral nature of the lesion. In 17-50% of patients, there is a need for amputation of the second lower limb.

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Diabetik oyoq sindromi rivojlanishining patogenetik jihatlari

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ABSTRAKT

Hozirgi kunda dunyoda diabetik oyoq sindromini davolash sohasida juda ko'p yutuqlarga erishildi, davolashda multidisipliner yondashuvlar ishlab chiqildi. Biroq, barcha yutuqlarga qaramay, diabetda oyoq amputatsiyalari soni ortib bormoqda. Dunyoda har soatda qandli diabetga chalingan 55 bemor pastki qismlarini yo'qotadi, iqtisodiy jihatdan rivojlangan mamlakatlarda esa har 100 ming aholiga 13,7 dan 32,3 gacha o'zgarib turadi, bu esa o'z navbatida o'lim darajasining yuqori bo'lishi, davolanish va reabilitatsiya xarajatlari bilan birga keladi. Tadqiqotlar shuni aniqladiki, yara jarayonining jarayoni tananing turli biologik reaktsiyalarining dinamik o'zgarishi bilan birga bo'lib, bu yaraning silliq shifo topishini yoki turli xil asoratlarni rivojlanishini belgilaydigan ko'plab endogen va ekzogen omillarning ta'siri ostida sodir bo'ladi. Mutaxassislarning yechimini talab etadigan bugungi kunda dolzarb muammolardan biri bu rivojlangan mamlakatlar aholisida uchraydigan qaddli diabet oyoq sindromi bilan murakkablashgan qandli diabetli bemorlarda jarrohlik-davolash tadbirlarining samaradorligini oshirish immunopatogenetika mexanizmlarini ishlab chiqishdir.

Ushbu sharh maqolasi diabetik oyoq sindromi rivojlanishining patogenetik jihatlariga bag'ishlangan.

Kalit so'zlar: qandli diabet, diabetik oyoq sindromi, patogenez

Патогенетические аспекты развития синдрома диабетической стопы

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АБСТРАКТ

В настоящее время в мире многое достигнуто в области лечения синдрома диабетической стопы, разработаны мультидисциплинарные подходы к лечению. Однако, несмотря на все достижения количество ампутаций ног при диабете растёт. Каждый час в мире 55 больных диабетом теряют нижнюю конечность, а в экономически развитых странах варьирует от 13,7 до 32,3 на 100 тыс. населения, что в свою очередь сопровождается высоким уровнем смертности, затратами на лечение и реабилитацию. Исследованиями установлены, что течение раневого процесса сопровождается динамичной сменой многообразных биологических реакций организма, подверженных влиянию большого количества как эндогенных, так и экзогенных факторов, которые определяют гладкое заживление раны или развитие различных осложнений. Одной из актуальных проблем на сегодняшний день, требующая от специалистов необходимости своего решения, является разработка иммунопатогенетических механизмов повышения эффективности, проводимых оперативных и лечебных мероприятий у больных сахарным диабетом осложненный синдромом диабетической стопы встречающихся среди населения развитых стран мира.

Данная обзорная статья посвящена патогенетическим аспектам развития синдрома диабетической стопы.

Ключевые слова: сахарный диабет, синдром диабетической стопы, патогенез