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THE STATE OF REGIONAL BLOOD FLOW IN DIABETIC FOOT SYNDROME


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ДИАБЕТИК ТОВОН СИНДРОМИДА РЕГИОНАР ҚОН АЙЛАНИШИНИНГ ҲОЛАТИ

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СОСТОЯНИЕ РЕГИОНАРНОГО КРОВОТОКА ПРИ СИНДРОМЕ ДИАБЕТИЧЕСКОЙ СТОПЫ

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Резюме. *Қандли диабет (ҚД) дунёда бир мунча муҳим бўлган ноинфекцион касаллик сифатида тан олинган бўлиб, тарқалиши жиҳатидан пандемия кўринишида тус олди. ҚДнинг кечки асоратларидан бўлган диабетик товон синдроми кўп учраб, юқори леталлик ҳамда эрта инвалидликка сабаб бўлмоқда. Қандли диабет касаллиги 2019 йилда 1,5 миллион ўлим ҳолатларига сабаб бўлиб, уларнинг 48% 70 ёшгача бўлганлар ташкил этган. Халқаро диабет федерацияси маълумотларига кўра, қандли диабет билан госпитализация бўлганларнинг 25% дан 47% тўқималар сурункали ишемияси туфайли ривожлаган товонлардаги йирингли деструктив зарарланишлар оқибатида бўлганлиги қайд этилган. Адабиётлар шархида диабетик товон синдромида микроциркуляциянинг бузилишининг асосий патофизиологик механизмларии ёритилган бўлиб, булар ўз навбатида пастки муччалар критик ишемиясига олиб келади.*

Калит сўзлар: *қандли диабет, диабетик товон синдроми, микроангиопатия, макроангиопатия, ишемия, микроциркуляция.*

Abstract. *Diabetes mellitus (DM) in the world is recognized as one of the most important non-communicable diseases, the spread of which has acquired the character of a pandemic. Diabetic foot syndrome leads the list of late complications of diabetes, leading to early disability and determining a high mortality rate. In 2019, diabetes was the direct cause of 1.5 million deaths, and 48% of all diabetes-related deaths occurred before the age of 70. According to the International Diabetes Federation, from 25 to 47% of hospitalizations of patients with diabetes are associated with purulent-destructive lesions of the feet due to the development of chronic tissue ischemia. The review reflects the main pathophysiological mechanisms of microcirculation disorders in diabetic foot syndrome, leading to critical ischemia of the lower extremities.*

Keywords: *diabetes mellitus, diabetic foot syndrome, microangiopathy, macroangiopathy, ischemia, microcirculation.*

Diabetic foot syndrome (DFS) is a severe complication of diabetes mellitus (DM), a manifestation of purulent-necrotic complications in the lower extremities, developing in 30-60% of patients [1, 2]. The importance of the problem of this complication is due to the fact that DM disease is steadily progressing worldwide. WHO reports that by 2025, the number of patients diagnosed with diabetes in the world will reach 300 million people [3].

In 2019, diabetes was the direct cause of 1.5 million deaths, and 48% of all diabetes-related deaths occurred before the age of 70. From 2000 to 2016, premature (i.e. under the age of 70) mortality from diabetes increased by 5%. In high-income countries, the rate of premature mortality from diabetes declined from 2000 to 2010, but then increased again in 2010-2016. In lower-middle-income countries, an increase in premature mortality from diabetes occurred in both of these periods [4].

In Russia, according to the registry of the NMRCTPM (National Medical Research Center for Therapy and Preventive Medicine) of Endocrinology, the number of patients with diabetes mellitus as of 2020 was 4.8 million people, 264 thousand of them had type 1 diabetes, 4.5 million - type 2 and 101 thousand – other types. As of 2018, out of 4.58 million diabetics, the majority (4.45 million) were adults [5].

In Uzbekistan, the number of patients with diabetes mellitus in 2020 amounted to 257,457, including 3,263 children and adolescents under the age of 18 [6]. Almost 25-30% of DM patients are diagnosed

for the first time in a surgical hospital, where they turn for purulent-necrotic processes of various localization, that is, with DFS [7]. According to the criteria of the International Agreement on Diabetic Foot (International Consensus on the Diabetic Foot, 2007), DFS is diagnosed in 4-25% of all patients with diabetes. Annually, new cases account for 2.2-5.9% of the patient population [7].

According to the International Diabetes Federation, from 25 to 47% of hospitalizations of patients with diabetes are associated with foot damage [9]. Every year in the USA and Great Britain 50,000-75,000 patients with DM are hospitalized for trophic ulcers of the lower extremities, which is from 2 to 7.2% of the entire population of patients with DM [10].

The social importance of DFS is determined by the fact that it leads to early disability and death [2, 4, 11]. Purulent-necrotic complications of DFS in 36 out of 1000 patients with DM pose a threat to life and become indications for amputation [12]. According to statistics, the development of ulcerative defects on the foot precedes 85% of all amputations in patients with type 2 diabetes. The risk of amputation in patients with DFS is 25 times higher than in the general population [13]. After studying the long–term consequences of amputation, it was found that postoperative mortality reaches 6%; within 5 years - 39-68 %; in the future, there is a need to perform amputation of the second limb within three years in 42% of patients [14].

DFS is an immediate threat to the development of ulcerative-necrotic processes and gangrene of the foot and combines pathological changes in the peripheral nervous system, arterial and microcirculatory bed, bone and joint apparatus [15]. The incidence of ulcers on the feet, according to many authors in the USA and the UK, ranges from 5 to 10.2% [16]. More than 40% of non-trauma-related limb amputations are carried out due to the development of diabetic gangrene, and mortality as a result of high amputations of the lower extremities reaches 25-50% [17].

In the foreign medical literature, since the mid-50s of the last century, changes in the feet of patients with DM have been designated by the term "diabetic foot". For a long time, patients with diabetic angiopathy were treated with the same surgical tactics as patients with chronic arterial insufficiency of the lower extremities. Subsequent analysis showed a difference in the duration and quality of life after amputation in patients with and without DM. In 1987, in Geneva, WHO specialists identified diabetic foot syndrome as an independent manifestation of DM along with retinal nephropathy. In 1989, an international declaration was adopted in Saint Vincent, as a result of which the number of amputations in patients with DM was halved in many countries of the world [18, 19, 20].

The main document on DFS is currently considered to be the International Agreement on Diabetic Foot (2007). According to this document, DFS 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 [21].

Consequently, DFS is primarily purulent–destructive lesions of the lower extremities due to diabetes. About 85% of these lesions are trophic ulcers of the foot, 15% are abscess, phlegmon, osteomyelitis, tendovaginitis, purulent arthritis and other processes that develop as a complication of a trophic ulcer or primary (without primary ulcer) [22]. In addition, non–purulent destructive lesion of the extremities - diabetic osteoarthropathy Charcot belongs to DFS. This group includes patients with stable consequences of the described processes as a result of amputations of limbs at different levels [22, 23].

The classical pathogenetic triad of DFS includes ischemia, neuropathy and infection. All these factors can lead to the development of DFS both independently and in combination for other reasons. Based on the predominance of one or another factor, there are 3 forms of DFS: neuropathic (60-75%), neuroischemic (20-30%) and ischemic (5-10%) [24]. In many studies of purulent-necrotic complications of DM, it is suggested not to separate the ischemic and neuroischemic forms, since the ischemic form (without signs of neuropathy) is rare, and the presence of ischemia is a determining factor for the prognosis and treatment of patients [25]. Therefore, taking into account the presence of ischemia in patients with DFS, in order to prevent the phenomena of necrobiosis in the tissues of the lower extremities and the development of complications, it is important to determine the tactics of treatment of patients with this pathology and prevent amputation to understand the mechanisms of microcirculatory changes in DFS.

Obliterating atherosclerosis of the vessels of the lower extremities is common and is observed at a younger age in DM [26]. For atherosclerosis, a multisegmental diffuse lesion of the popliteal segment, the tibial artery and the arteries of the foot is typical, the ilio-femoral segment is less often affected [25]. Micro-preparations with microangiopathies show thickening of the basement membrane, its splitting into layers, between which collagen fibers are determined. These changes in the capillary walls lead to a decrease in their lumen and subsequent obliteration [26].

In addition, the phenomenon of hyperglycemia leads to non-enzymatic glycation of body proteins, which complicates tissue oxygenation and leads to hypoxia and microcirculation disorders described above. Hyperglycemia aggravates blood rheology: the adhesive properties of platelets and erythrocytes increase, blood viscosity and blood flow rate slows

down. In the future, there is a loss of elasticity of the walls of erythrocytes and platelets, a violation of their osmotic resistance due to changes in physicochemical properties [14, 21]. These disorders contribute to increased hemolysis, aggregation and destruction of platelets as they pass through the capillaries, which leads to mechanical damage to the endothelium and the development of disseminated intravascular coagulation syndrome. Hemolysis products are an activator of lipid peroxidation. This provokes the formation of a large number of aldehydes and ketones, which in turn lead to a change in the antigenic properties of lipoproteins with the formation of autoantibodies. Against the background of hyperglycemia, there is a violation of the binding of insulin by endotheliocyte receptors. The amount of laminin and fibronectin, which ensure the attachment of endotheliocytes to the basement membrane, also changes [27]. In places of intensive blood flow, defects in the intercellular connections of the endothelium occur, which leads to an increase in the permeability of capillaries. Histologically, plasmorrhagia with endothelial proliferation and hyalinosis is detected. The accumulation of low-molecular (IgG, p–lipoproteins, albumins), subsequently high-molecular proteins, up to fibrinogen, is determined in hyaline masses [28].

With concomitant atherosclerosis, lipogranulomas are formed in muscle-type arteries, consisting of foamy smooth myocytes and macrophages prone to decay. The thickness of the elastic-muscle type media vessels is significantly reduced, a significant amount of PAS-positive material and a decrease in the level of acidic glycosaminoglycans are detected in it. Also, a characteristic complication of DM is calcification of the media arteries (Menkeberg atherocalcinosis) of medium and small diameter, which increases the risk of amputation, according to some studies, by 5.5 times [29].

It should be noted that with obliterating atherosclerosis of the vessels of the lower extremities, large diameter arteries are affected, which distinguishes the morphology of the lesion of the arterial bed in this disease. Frequent detection of IgG in the vessels together with complement indicates participation in the formation of diabetic microangiopathy and immune mechanisms. Circulating immune complexes are adsorbed on endotheliocytes, causing their damage with violation of the endothelial lining and basement membrane and increased vascular permeability. In the presence of a weak antigen, small antigen – antibody complexes circulate in the blood for a long time, provoking chronic damage to the vascular wall [30].

By the 80s of the XX century, the leading factor in the development of purulent-necrotic complications of DFS was the vascular theory, according to which macro- and microangiopathy were the main factors in their development. However, with the advent of methods of quantitative (ultrasound Dopplerography) and qualitative (partial oxygen pressure) assessment of blood flow, vascular theory lost its primacy under the pressure of a large number of observations with the presence of trophic ulcers against the background of satisfactory hemocirculation [1, 31]. According to domestic and foreign authors, the main etiological factor in the development of DFS should be considered hyperglycemia resulting from absolute or relative insulin deficiency [32, 33, 34].

Currently, there are several reasons for the development of DFS, forming a vicious circle: an increased blood glucose content entails glycolysis of plasma proteins, a change in their conformation and function. Such proteins are deposited in the walls of capillaries, reducing their lumen, resulting in a violation of the rheological properties of blood, which leads to the development of spontaneous microthrombosis. Also, an important link in the pathogenesis of diabetic microangiopathy in DFS is a deterioration in the rheological properties of blood and a violation of the platelet link of hemostasis [35-37]. Many pathological mechanisms (atherosclerotic and coagulological) are involved in the formation of macroangiopathy in patients with DM, which are currently united by the concept of "atherothrombosis". Its occurrence and development leads to a sharp decrease in blood circulation in the affected limb, creating conditions for the development of critical ischemia [38-41].

Ischemia in diabetic angiopathy has a long progressive character and manifests itself most often after external influences, such as trauma. This is due to the fact that the processes of vital activity of the soft tissues of the lower extremities are characterized by a lower partial pressure of oxygen than for active inflammation or repair. A decrease in oxygen concentration in the skin and subcutaneous tissue, along with hyperglycemia, leads to atrophy and a decrease in the protective properties of tissue macrophages. An adequate response of the body to injury is an increase in blood flow to the damaged area of the skin. However, patients with DM are characterized by the presence of an open arteriovenous precapillary shunt, as a result of which, bypassing the capillary bed, blood enters the venous system, impoverishing peripheral blood flow. A.J.M. Bulton described this phenomenon for the first time in 1982 [42, 43]. Endothelial dysfunction is also the cause of thrombosis (mainly of the capillary bed) in patients with DM. Thickening of the capillary basement membrane is a structural manifestation of microangiopathy. These changes depend on the level and duration of hyperglycemia [44]. A change in the basal membrane of the vessel leads to a violation of leukocyte migration, which manifests itself by reducing the effectiveness of the inflammatory reaction in the area of the lesion [45].

Consequently, the regional blood circulation of the extremities is the total value determined by the degree of violation of the main, collateral blood flow and the state of microcirculation. To determine the tactics of complex treatment and the prognosis of limb preservation in a patient with DFS, the blood flow of the main vessels of the lower extremities is traditionally determined. However, at present, increasing importance is attached to the assessment of the parameters of the microcirculation system, since it is in this department of the cardiovascular system that blood flow is regulated in accordance with the metabolic needs of tissues. The failure of capillary circulation is one of the leading factors in the development of gross trophic disorders in patients with decompensation of collateral blood flow.

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СОСТОЯНИЕ РЕГИОНАРНОГО КРОВОТОКА ПРИ СИНДРОМЕ ДИАБЕТИЧЕСКОЙ СТОПЫ

Давлатов С.С., Хамдамов Б.З.

Резюме. *Сахарный диабет (СД) в мире признан одной из наиболее важных неинфекционных болезней, распространение которой приобрело характер пандемии. В списке поздних осложнений СД лидирует синдром диабетической стопы, приводя к ранней инвалидизации и определяя высокий уровень летальности. В 2019 г. диабет стал непосредственной причиной 1,5 миллиона случаев смерти, и 48% всех связанных с диабетом случаев смерти произошли в возрасте до 70 лет. По данным Международной диабетической федерации, от 25 до 47% госпитализаций больных СД связано с гнойно-деструктивными поражениями стоп вследствие развития хронической ишемии тканей. В обзоре отражены основные патофизиологические механизмы возникновения нарушения микроциркуляции при синдроме диабетической стопы, приводящие к критической ишемии нижних конечностей.*

Ключевые слова: *сахарный диабет, синдром диабетической стопы, микроангиопатия, макроангиопатия, ишемия, микроциркуляция.*