

THE REVIEW OF THE FORM OF NEUROPATHIC DIABETIC FOOT Davlatov S.S.

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Abstract: *the review addresses the issues of etiology and pathogenesis, classification and treatment of such complications of diabetes mellitus as diabetic foot syndrome (DFS). The role of micro- and macroangiopathy, peripheral diabetic neuropathy, foot deformities and infection of damaged tissues as the main factors in the development of DFS is characterized.*

Keywords: *diabetic foot syndrome, purulent-necrotic complications, treatment.*

In international agreements on the diabetic foot [4], the definition of a diabetic foot was proposed as 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 [16]. Today, diabetic foot syndrome (DFS) is understood as all pathological changes in the peripheral nervous system, arterial and microcirculatory bed, which pose an immediate threat to the development of ulcerative necrotic processes and gangrene of the foot [31].

Based on modern definitions of DFS, the main risk factors for its development are: distal diabetic polyneuropathy; peripheral arterial disease in the stage of critical ischemia; deformity of the feet against the background of distal polyneuropathy; diabetic retinopathy with a significant decrease in visual acuity; lack of adequate foot care [11].

In this case, the main pathogenetic factors leading to the formation of wounds on the foot are trauma, deformation and ischemia, both in isolation and in combination with each other [7].

For many years, the pathogenetic classification of diabetic foot syndrome has been used in clinical practice [23]:

1. Neuropathic form:
 - without osteoarthropathy;
 - diabetic osteoarthropathy.
2. Neuroischemic form (mixed form).
3. Ischemic form.

Recently, neuroischemic and ischemic forms of DFS have been combined into one group, in accordance with the main pathogenetic factor - ischemia, which accounts for up to 40-50% of patients with diabetic foot syndrome [6]. The pathogenetic classification can only be used to describe the most general points in the diagnosis and treatment of patients with diabetic foot syndrome [18]. In this regard, the development of unified classifications based both on

pathogenetic forms and on the staging and depth of damage to the tissues of the foot has been engaged in for more than a quarter of a century. One of the original such classifications was the classification recommended back in 1976 by B. Meggitt and introduced into wide clinical practice by F.W. Wagner in 1981 [28, 30].

In 2004, the MEASURE system was proposed [12], where M - defect measurement (length, width, depth, and area), E - exudate (quantity and characteristics), A - type of wound (wound bed, presence of necrosis), S - severity of pain, U - destruction (presence or absence), R - regular monitoring of all parameters, E - condition of the edges of the wound and surrounding skin.

Diabetic foot syndrome is a late complication of diabetes mellitus. Wound defects in this complication are chronic defects and therefore difficult to treat [19]. There is a violation of the pathophysiological mechanism of repair, the wound process takes a protracted chronic course with a slowdown in the healing time [16]. Diabetic polyneuropathy develops against the background of chronic hyperglycemia and insulin deficiency, which lead to the activation of the non-insulin-dependent polyol pathway with increased accumulation of end metabolic products in Schwann cells of peripheral nerves - sorbitol and fructose (polyol shunt) [5]. Glucose is converted to sorbitol (polyol) by aldose reductase using NADPH as a coenzyme. The accumulation of sorbitol in hyperglycemia leads to an imbalance in the metabolism of phosphoinositide and damage to coenzymes, which has a significant effect on the development of diabetic polyneuropathy [18]. Another important metabolic factor is myo-inositol metabolism disorder. The latter is one of the proteins that support the stabilization of cell membranes and are involved in the rate of conduction of impulses through the nervous tissue [10]. A decrease in the content of myo-inositol in axonal tissue even by 10% leads to a significant decrease in the use of energy by the neuron. Non-enzymatic and enzymatic glycosylation of proteins - myelin and tubulin (structural components of nerve fiber), lead to demyelination and impaired nerve impulse conduction; glycosylation of proteins of the basement membrane of capillaries causes its thickening and disturbance of metabolic processes in nerve fibers [10].

One of the early hypotheses for the development of diabetic polyneuropathy was the vascular theory, according to which dysfunction of the endothelium of the microvasculature supplying blood to peripheral nerves is the main cause of nervous disorders in diabetes [17]. Denervation of epineural arteriovenous shunts leads to the discharge of arterial blood through them, bypassing the microvasculature. This leads to a decrease in perfusion and ischemia at the level of endoneural capillaries [12].

Motor polyneuropathy, which results in demyelination of distal motor fibers, contributes to atrophy and loss of function of the small internal muscles of the foot, anterolateral muscle group of the lower extremities, and the dominance of long flexors - flexors of the fingers, plantar flexors and ankle extensors. In this

regard, characteristic deformities of the feet and fingers appear (flat feet, hammer-like and claw-like fingers, plantar protrusion of the heads of the metatarsal bones), which can form pathological areas of excess pressure - zones where normally there should be no increased pressure during walking (tops of the toes, dorsum of interphalangeal joints, projections of the metatarsal heads) [5].

Autonomic neuropathy leads to decreased sweating and, as a result, dry skin [30]. When walking, in this case, minor injuries (cracks) can form, which become infected and turn into chronic wounds. Autonomic neuropathy plays an important role in the regulation of peripheral blood flow. In patients with diabetes mellitus with diabetic polyneuropathy, autosympatectomy occurs [7]. Autonomic neuropathy causes a loss of vasomotor tone, leads to increased blood flow in the superficial vessels of the skin, which causes an increase in the temperature of the skin of the feet, increased blood circulation and contouring of skin veins even in the horizontal position of the patient. The presence of autonomic neuropathy changes intraosseous blood flow, stimulating osteoclastic activity, resorptive processes in the bone structures of the foot, causing the development of local osteoporosis [5, 21].

The development of motor neuropathy with the formation of the characteristic deformities described above leads to sprains and instability in the joints. The severe calciuria present in diabetes mellitus and the loss of salts, which can increase their intake, also contributes to the development of diabetic osteoarthropathy (DAP) [3]. An important point in the development of DOAP is considered to be hormonal imbalance. Insulin is directly involved in the process of bone remodeling. This hormone, along with parathyroid hormone, calcitonin and growth hormone, regulates the activity of bone cells. It has been proven that insulin has both a direct effect on bone tissue and indirectly through an effect on the production of insulin-like growth factor in the liver [16]. Dislocation or fracture of the foot bones is considered the initiating or starting moment for the formation of Charcot's foot [9]. Due to the presence of sensory neuropathy in half of the patients, this is not accompanied by painful symptoms or, more precisely, the latter does not correspond to the severity of changes in the osteoarticular apparatus. The presence of osteoarthropathy contributes to the development of wounds. DOAP does not develop in patients with impaired blood supply to the lower extremities [18]. Ischemia may play the role of a kind of "protection" factor against accelerated blood flow and intracapillary hypertension, which can trigger the process of bone resorption and the occurrence of microtrabecular fractures [13]. The main clinical manifestations of the neuropathic form of diabetic foot syndrome are sensory impairment, dryness of the skin of the feet, the formation of callosities and microtraumas, chronic wounds and non-infectious destruction of bones and joints - diabetic neuroosteoarthropathy or Charcot's foot [5, 31]. It is wounds that are the most common and threatening limb loss condition of the neuropathic form of the

diabetic foot due to the addition of a secondary infection and the development of a purulent-necrotic process, and even sepsis [26].

Typical complaints presented by patients with diabetic neuropathy are complaints of dull, aching pain in the feet, legs, aggravated at rest. These pains force to change the position of the body, to move. Also worried about paresthesias in the lower extremities, manifested in the form of unpleasant sensations experienced without receiving irritation from the outside: a feeling of numbness, creeping, cold or heat, burning, etc. With the predominance of peripheral motor disorders, complaints of rapid fatigue of the lower extremities, muscle weakness and difficulty in dorsal or plantar flexion of the feet [29]. Often, chronic wounds form at points of excess plantar pressure due to foot deformities. Diagnosis in DFS includes the collection of anamnesis: the duration of diabetes mellitus, hyperglycemia, the nature of drug therapy, a history of defects in the feet and previous surgical interventions, diseases of the cardiovascular system (arterial hypertension), dyslipidemia, retinopathy and nephropathy. Living conditions, alcohol and smoking abuse are also assessed. Examination of the feet, assessment of the neurological status, the state of arterial blood flow and the musculoskeletal system, laboratory and instrumental diagnostics, measurement of the distribution of plantar pressure are performed [2].

In laboratory diagnostics, they perform - determination of the level of glycemia, the level of glycosylated hemoglobin (HbA1c), the presence of glucose and ketone bodies in the urine, an increase in the level of cholesterol (triglycerides), fibrinogen, APTT and TB. In the presence of a wound defect, bacteriological studies, histological studies of the operating material are necessary [19].

Diagnostics of neuropathy - includes the assessment of complaints on the TSS and NSS scales (indicators of neuropathic symptomatic counting), the study of pain, tactile, vibration and temperature sensitivity (needle prick on the plantar surface of the first toe, 10 g monofilament, graduated tuning fork, biothesiometry), their score on the NDS scale (neuropathic dysfunctional score), as well as the assessment of tendon reflexes, electromyography [16, 21].

The main principles of local treatment of chronic wounds in patients with diabetic foot syndrome are the conditions of moist healing, the absence of excessive accumulation of exudate, the rejection of the use of antiseptic agents that have a destructive and toxic effect, and gentle mechanical treatments [20].

Sanitation of wounds with antiseptic solutions must meet certain requirements: it is necessary to withstand a certain exposure of the drug to obtain an antimicrobial effect, taking into account the possible toxic effect [27]. When using a 3% solution of hydrogen peroxide, a cytotoxic effect on granulation tissue and fibroblasts has been proven, therefore, the use of a 1.5% solution is recommended. It is considered safe to use a 0.05% aqueous solution of chlorhexidine and 0.01% miramistin solution, as well as saline [14].

For wounds with abundant purulent discharge and tissue detritus, ultrasonic cavitation treatment with a 0.02% aqueous solution of chlorhexidine is indicated (mechanical cleaning of the wound, reduction of bacterial contamination, improvement of regional microhemodynamics), the use of air-plasma flows (exogenous NO-therapy) [21]. Currently, there is no doubt about the need to use dressings for the treatment of chronic wounds. Full and accelerated epithelialization of chronic wounds is largely determined by the competent use of modern dressings [19]. These funds must meet the following requirements: non-invasiveness; providing moist wound healing; preventing secondary wound infection; ensuring adequate drainage; creating an ideal microclimate for wound healing (gas exchange, heat exchange); the possibility of anatomical modeling of a wound defect [24].

When choosing a dressing, the stage of the wound process should be taken into account. So in the phase of exudation it is recommended to use alginates and polyurethane foam dressings [35]. In the phase of proliferation and epithelization, it is advisable to use hydrocolloids, hydrogels, collagen-containing materials [11].

The most important aspect of the treatment of chronic wounds in patients with diabetic foot syndrome is the control of wound infection. The first stage is the complete removal of necrotic and non-viable tissue by a surgical method [7]. In the neuropathic form of DFS, surgical treatment must always be radical. In superficial lesions (I-II degree according to Wagner), the scope of surgical treatment consists in removing necrotic soft tissues, excision of hyperkeratosis surrounding the wound, careful revision of the defect cavity for the presence of additional pockets, leaks and adherence of bone structures [4].

Despite the generality of approaches to the local management of patients with DFS, each individual patient requires an individual approach. In many cases, it is the competent use of modern dressing materials that is the fundamental link in achieving a positive treatment result [40].

One of the main conditions for the healing of a wound located on the foot is the unloading of the affected area. It allows, first of all, to exclude wound trauma, and also to reduce the likelihood of re-infection [26]. At present, the difficult bed rest is replaced by various options for unloading devices, of which the most accessible are removable ("half-shoe", CastWalker), an individual unloading dressing (IRP) Total Contact Cast (TCC), which can be used in removable and non-removable modifications. The International Working Group of IRI TSS has been defined as the preferred method of unloading the limb in patients with neuropathic DFS [11]. With the introduction of standards for the treatment of DFS, the question no longer arises whether unloading of the limb is necessary, now it is important to choose the optimal type of unloading or modification of the TCC for a particular patient, evaluating not only the clinical situation, but also adherence to treatment, the social status of the patient.

Additional factors influencing the choice of the unloading method are the

professional training of medical personnel in the manufacture of IRP TSS and the financial capabilities of the medical institution or patient [22].

The healing process of a chronic wound is a complex mechanism consisting of a whole cascade of morphological changes occurring in the wound. Understanding the mechanisms of interaction and function of various cells involved in the healing of a wound defect can help in the creation of new innovative, highly effective methods of treating wounds and preventing complications in their course [32].

In recent years, a number of active drugs have been created for the local treatment of wounds of various origins and localization [1, 17].

The principle of wet wound healing is dominant. Many techniques and dressings have been proposed for the healing of chronic wounds. However, only the right level of moisture can help keep the wound area hydrated and provide vital substances to support healing. On the other hand, too much effusion can interfere with the wound healing process. The greatest difficulty is the treatment of wounds with a slow course of the reparative process, a high risk of purulent complications in the postoperative period. In such cases, coatings based on bioabsorbable polymers containing antimicrobial components are used [30]. Among biological implants, the most promising is the fibrillar protein of the connective tissue, namely, collagen [7, 28].

Collagen, the main structural protein, makes up approximately one third of the body's total protein. Due to the shape of the protein molecule, collagen is referred to as fibrillar proteins. Although collagen is widely distributed in the body, treated dermis, tendons, and dura mater of humans and animals containing it are commonly used for medical purposes [2].

The filtration and barrier properties of collagen membranes play an essential role in medicine [13, 17]. It has been proven that the physical and chemical properties of collagen fibers are directly related to the polymerization of tropocollagen, the binding of its molecules together by groups and covalent intermolecular bonds [14].

Collagen-based implants combine many of the benefits of various synthetic and biological implants. The main advantages of using collagen as a biomaterial are based on its high biocompatibility, low immunogenicity, and easy control over its biodegradation. Numerous studies have proven the ability of collagen to contact and guide cells in order to restore normal tissue anatomy [10]. At the same time, studies have demonstrated the importance of collagen contact with the inner surface of the wound for the epithelialization process. Collagen type 1 provides targeted contact for epithelial cells and fibroblasts, creating optimal cell migration and orientation [30]. Collagen's job is to bind cells together, allowing them to form new tissue. When this implant binds to the wound, fibroblasts from the surrounding tissue migrate to and enter the implant. They produce new collagen fibers that fill the wound in the implantation site, allowing new healthy tissue to grow. The implanted collagen matrix is slowly absorbed

during the epithelialization process [20]. Collagen implants provide damaged tissues with the main biological substrate that is required for healing - a natural, connective tissue specific collagen resource.

The accumulated experience in the use of collagen materials in various tissue repair procedures has led to the creation of a resorbable collagen-based implant for the regeneration of connective tissue [25]. This material is capable of being a safe and effective agent for tissue repair [6]. The potential effectiveness of the use of such materials comes down to several factors: the ability to provide a suitable substance for cell adhesion and proliferation, the formation of a supporting structure of the extracellular matrix, and wound resorption in a controlled manner [28]. In addition, the materials should have minimal toxicity, elasticity and low immunogenicity, similar to intact tissue.

Recently, platelet-rich autoplasm has been actively used in various fields of medicine. Platelets, known for their role in hemostasis, have another very important physiological function that has only recently been discovered and studied: they are carriers of proteins that play a role in tissue regeneration. Platelets contain growth factors that are responsible for the regeneration and repair of various tissues. They are carriers of these factors and release them in places where damage has occurred [1, 23]. Growth factors enclosed in special secretory platelet granules - alpha granules include: platelet growth factor (PDGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), platelet angiogenic growth factor (PDAF), transforming factor growth (TGF-P) [24]. The release of these factors is triggered by the activation of platelets by various stimulant substances such as thrombin, calcium chloride or collagen. Growth factors play a key role in wound healing and regenerative processes such as chemotaxis, proliferation, differentiation, and angiogenesis [10].

The technology for the production of platelet-rich autoplasm makes it possible to increase the concentration of these factors. In addition, other substances (fibronectin, vitronectin, sphingosine, 1-phosphate, etc.) are also present in the plasma, which play an important role in wound healing. Recently, the morphological and molecular configuration of platelet-rich autoplasm has been recognized, a network of fibrin around platelets that supports the regenerative matrix [15]. Since platelet-rich autoplasm contains growth factors, it is able to stimulate angiogenesis and increase fibroblast differentiation, accelerating wound healing and reducing the risk of rough scar formation [7]. Platelet growth factor (PDGF) and epidermal growth factor (EGF) are the main factors influencing fibroblast migration, proliferation and collagen synthesis [5]. According to the literature, increased concentrations of these factors accelerate wound healing by 2-3 times [8]. According to hematological criteria, platelet-rich autoplasm is plasma containing 1 million platelets per μl [27].

Recently, there are a number of publications devoted to the use of platelet-rich autoplasm in the treatment of chronic wounds of the lower extremities in

the form of injections and applications against the background of chronic venous and arterial insufficiency [26]. The results of the research allow us to conclude that the use of platelet-rich autoplasm in the complex local treatment of chronic wounds provides a wide range of local and systemic therapeutic effects, thereby improving the results and significantly reducing the time of epithelialization. The experience of using platelet-rich autoplasm in combination with a collapon for periodontitis in dentistry is described [1], in the local treatment of chronic wounds against the background of venous pathology of the lower extremities with other collagen-containing biologically active drugs [5]. This combination improves the results and shortens the treatment time compared to the separate use of drugs.

The development of new methods of local treatment of chronic wounds against the background of the neuropathic form of diabetic foot syndrome, which combines the sanogenetic factors of collagen and platelet-rich autoplasm, seems promising.

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