**MODERN PROBLEMS OF TREATMENT OF PATIENTS WITH DIABETIC FOOT SYNDROME (LITERATURE REVIEW)**

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**Abstract**

Diabetes mellitus (DM) is a significant medical, social, and economic issue, leading to disability, reduced quality of life, early disability, and increased mortality. The aim of this review was to systematically search for scientific information on diabetes mellitus, its complication in the form of diabetic foot syndrome, and its treatment. The review included studies from 2006 to 2022, sourced from Medline, UptoDate, Google Scholar, Cochrane, and PubMed databases. A total of 40 relevant sources were analyzed. The review highlighted the increasing number of diabetes patients worldwide, making the issue of diabetic foot syndrome highly relevant. Treatment of diabetic foot syndrome requires a comprehensive approach that addresses hyperglycemia, ischemia, neuropathic pain, and trophic disorders. Based on the analysis of domestic and international literature, it is concluded that treatment of diabetic foot syndrome must be multidisciplinary, involving various specialists, as diabetic foot and related complications, such as foot ulcers and infections, are the leading cause of hospitalization in diabetic patients.

**Key words:** diabetes mellitus, diabetic foot syndrome, trophic disorders.

**Introduction**

Diabetes mellitus (DM) is of great importance in the world in terms of its medical, social, economic significance, leading to disability, reduced quality of life, early disability and death.

According to the International Diabetes Federation, 537 million people will have DM in 2021. Globally, 45.8% of all adult diabetes cases, or 174.8 million people, are undiagnosed, ranging from 24.1% to 75.1% according to regional data. 83.8% of undiagnosed diabetes cases occur in low- and middle-income countries.1

In the Republic of Kazakhstan every year there is a steady increase in the number of patients with diabetes mellitus, currently the total number is more than 400 thousand people. Over the past 10 years, the number of patients in the country has increased 2-fold. According to the Ministry of Health, as of 1 July 2022, there are 439,327 people with diabetes mellitus on dynamic control, including 26778 people diagnosed with type 1 DM (21989 adults and 4789 children). Type 2 diabetes - 412,549 people (412,206 adults and 343 children).

**The aim of the study** is to systematically search for scientific information about diabetes, its complications in the form of diabetic foot syndrome and its treatment.

**Search strategy:** The search for scientific publications on the proposed topic was conducted in databases of evidence-based medicine (PubMed, Scopus, Cochrane Library, Medline), electronic scientific resources (e-Library, Cyberleninka, medical websites of neighbouring countries), which allowed to identify about 3770 literature sources, of which 40 are included in this review, 22 of them in English. The depth of the search was 16 years (2006 - 2022). This is due to the importance of fundamental works of the beginning of the 21st century, revealing the main problems of pathogenesis and genetic bases of development of carbohydrate metabolism disorders in representatives of different ethnic groups at early stages of DM. No such studies involving ethnic groups have been conducted in the future.

Inclusion criteria: results of modern studies, carried out taking into account all the requirements of evidence-based medicine; data of fundamental basic research conducted in ethnically diverse groups; English- and Russian-language publications.

Exclusion criteria: ‘case report’; sources before 2006 that do not meet the requirements of evidence-based medicine; abstracts.

**Results of the work and their discussion:**

**Prevalence and incidence of diabetic foot syndrome.**

Diabetic foot syndrome (DFS) is a condition in which a diabetic patient with diabetes presents with a nidus of infection, ulceration and/or disruption of the deep tissues of the foot, including the amount of bone and joint involvement of the foot associated with neurological disorders, and/or decreased baseline blood flow in the arteries of the foot of varying degrees of severity.2 Diabetic foot syndrome is one of the most costly complications of diabetes.3

About 422 million people worldwide have diabetes, and about one third of them have an important risk factor for diabetic foot ulcer development, including poor foot sensitivity due to peripheral neuropathy and/or poor foot perfusion due to peripheral arterial disease.4

In developed and developing countries, one of the most debilitating and costly consequences of diabetes is diabetic foot ulcer (DFU) and related foot complications.4 An estimated 18.6 million (15.0-22.9) people worldwide currently have active DFU; an additional 131 million (1.77% of the world population) have risk factors for developing DFU if not addressed in a timely manner.5 It is estimated that one-third of all diabetes-related costs go to diabetic foot care in the United States, with two-thirds of these costs attributable to inpatient care, representing a significant cost to society.6 The consequences of DFU are not limited to amputation. DFU can put patients at risk for other side effects such as falls, fractures, reduced mobility, weakness, and death. For example, diabetes-related mortality after amputation is 70% after 5 years, which surpasses many common cancers such as breast and prostate cancer.7 Although DFU is successfully treated, patients can often suffer from significant leg muscle atrophy, resulting in early weakness and reduced mobility.8

The impending epidemic of diabetes and the high prevalence of DFU and related complications make it clear that there is a need for increased prevention of DFU. At least 70% of amputations can be prevented.9 Randomised controlled trials(RCTs) and meta-analyses show that with interventions such as proper foot (sole) care, proper shoe care, daily foot temperature monitoring and treatment,10,11,12 DFU can be prevented by controlling these major reversible risk factors. However, there is still a high incidence and serious complications of diabetic foot syndrome worldwide, highlighting the need for further research into the management of this pathology.

**Modern approaches to the treatment of diabetic foot syndrome.**

The main objectives in the treatment of diabetic foot syndrome are the treatment of ulcer defects, maintenance of the supporting function of the foot, foot, physical and social rehabilitation. Treatment of patients with ulcers is a very complex and long process, the rate of wound healing is very low.13 An important condition for the successful treatment of trophic ulcers in patients with neuropathic and combined DFU is to ensure complete emptying of the affected area.

In addition to relieving the affected area of the load, the first surgical treatment of the wound should be performed to eliminate all necrosis. Surgical, mechanical, ultrasound methods can be used. An important point in the treatment of trophic ulcers in patients with DFS is the monitoring of wound infection. After treatment, the wound should be closed with a sterile atraumatic dressing. In the presence of a foot ulcer, the initial treatment is carried out in a dressing room.

Analysing the spectrum of the most effective agents for local treatment and, accordingly, when immobilisation to dressings is possible, 5 main groups should be distinguished:

\* antimicrobial agents;

\* proteolytic ferments;

\* antioxidants;

\* analgesics;

\* reparacin stimulation

Choosing a local antimicrobial agent for the treatment of infection, the surgeon primarily relies on antiseptics. The main pathological processes in the wound in the I and II phases of the wound process are associated with wound infection and necrosis (infectious, vascular, mixed etiology).14,15 The use of antiseptic solutions accelerates the elimination of infection and prevents secondary infection.16 There are many antiseptics available for surgeon's choice and their efficacy against wound infection is supported by multinomial studies. But in practice, the antimicrobial properties of antiseptics may be offset by their negative possession on granulation development earlier.17,18 Complete destruction of pathogens can be easily achieved by physical or biological antiseptic techniques. But, for example, the use of high doses of radiation as an antiseptic agent is unacceptable to humans. The use of fly larvae requires the use of appropriate techniques, may cause a number of aesthetic problems and may be rejected by the patient as an effective wound healing agent.19,20

When choosing an antiseptic, preference is given to combined preparations against microflora of a broad spectrum of action. Currently, the optimal antiseptics are: povidone iodine, miramistin, chlorhexidine and others.8

Any ointment containing an antibiotic has potential advantages and disadvantages in the treatment of wound infection.21

The use of a topical form of antibiotic may be accompanied by increased antimicrobial resistance in any pathogens. However, if a topical antibiotic is not used regularly, the risk of resistance growth is significantly reduced.22 For example, bacitracin and mupirocin are not used systematically despite their fairly broad antibacterial spectrum, which makes them ideal for topical use in skin and soft tissue infections.23, 24

In cases of critical foot ischaemia, surgical treatment of the wound before revascularisation is dangerous, as it may lead to an enlarged area of necrosis. The first step is revascularisation of the affected foot with one of the available methods, followed by treatment of the purulent-necrotic focus on the foot. In case of an active infectious process (fibrillary fever, leukocytosis, purulent wound exudate, hyperaemia and hyperthermia of soft tissues of the affected area), systemic antibacterial therapy is indicated, taking into account the nature and sensitivity of the microflora.25

In recent years, vacuum therapy has been used in the treatment of DFS with complicated purulent-inflammatory process, although previously this method was used in the treatment of purulent wounds.26

This method is noteworthy because, as noted by V. V. Belov (2007), O. Belova et al. V. Belov (2007), O. Belova et al. (2014), Nartaylakov M. A. et al. (2017), Belov Yu. V. et al. Authors (2020) have a positive effect on the reparative processes of the wound under the influence of negative pressure, caused by a decrease in the level of bacterial fertility, acceleration of healing and constant course of the disease, creation of wound rest, improvement of microcirculation. The authors used this method in patients with DFS complicated by purulent-necrotic process and noted improvement of wound healing, especially after surgeries (amputations) performed due to complications of DFS, but this method requires special conditions and equipment, which is the reason why the possible method is rarely used.

Soluyanov M. Yu, and other authors (2021) in their work evaluated the effectiveness of using vacuum therapy as primary necrectomy in patients with trophic ulcers against the background of diabetic foot syndrome. The authors of the Wagner classification (Wagner M., 1980) studied 160 patients with diabetic foot syndrome 1-2 stages . Researchers concluded that the use of vacuum therapy as primary necrectomy of trophic wounds against the background of diabetic foot syndrome provides a closed moist wound environment, which prevents the spread of bacteria and the infectious process. This technical device increases the mobility and comfort of the patient, reduces the duration of his/her stay in hospital.27

According to a number of researchers, the difficulties, as well as the duration of treatment and its low effectiveness are associated with a significant decrease in resistance to infection, which contributes to the disruption of local tissue reactions, inhibition of immune mechanisms of regulation of the reporative wound process, high microbial seeding of the wound surface (V. V. Zavatsky, A. S. Navitsky, 2014; R. P. Terekhova et al., 2015; El-Aziz abd et al, 2010; E.P. Vanos et al., 2010; M.V. Shinllez, 2012).

In the treatment of DFS complicated by purulent-necrotic process, special attention should be paid to sugar-lowering and anti-inflammatory therapy (Shabunin et al., 2019; Y. Costa et al, 2006; B. Kulzer, 2006; E. Faglia et al., 2007). In this regard, the introduction of antibiotics is often used in various ways and, most importantly, they are prescribed taking into account the nature of the microflora and its sensitivity to antibiotics, since in this complication aerobic and anaerobic microflora and often insensitive to many antibiotics, so requires a special approach in the choice of antibiotics (M. I. Kuzin,B. M. Kostyuchenok, 2012).

Lymphotropic administration of antibacterial drugs and carboxytherapy is the optimal therapy in the treatment of surgical foot infections.

In case of microcirculatory disorders, it is a combined method of treatment, in all types of surgical infections, as well as against the background of concomitant pathology in middle-aged and elderly patients, facilitating the delivery of drugs to the localised area of the pathological process (by lymphotropic administration) and improving the blood supply of the affected segment (by carboxytherapy).28

There is a search for methods that provide maximum concentration of antibiotic in the lesion. Shvetsov D. A. (1996) used this method in acute nonspecific lung and pleura diseases and noted improved treatment results compared to the administration of traditional antibiotics.

Korovin A. Ya. and Baska authors (2012) used platelet-rich autologous plasma in the treatment of patients with DFS, tunnel space in musculofascial conditions of the lower leg. Application of this method in the complex of treatment of purulent complications made it possible to perform forced operations 2 times less often. The authors were able to reduce the frequency of high amputations, in most cases being limited to small amputations, to achieve a decrease in postoperative complications, but despite the good effect, the method has not been widely spread due to the complexity of preparing the blood cell mixture.

In the treatment of purulent-inflammatory diseases, the introduction of drugs into the femoral artery by puncture or through a catheter inserted into the artery for a certain period of time is used, which makes it possible to re-inject antibiotics or necessary drugs into the artery or to use regular drip injection. With intra-arterial injection, a high concentration of antibiotic and other drugs that improve tissue trophicity, microcirculation (novocaine, heparin, nosh-pa, trental, etc.) occurs in the pathological focus. But the method is unsafe, and it is not always possible to successfully puncture or catheterise the artery. Despite the positive results of treatment, puncture of the femoral artery in obese patients is difficult, in addition, the arterial wall may be damaged during puncture, haematoma occurs, which complicates the course of the disease, and nowadays intravenous administration of drugs for DFS is very rarely used.

In recent years, there have been reports of drug administration through small branches of the main arteries. Finally, for femoral artery catheterisation, drugs are administered through the inferior epigastric artery. This method in his work was used by Chakanov t. (2020) for DFS complicated with purulent-necrotic complications in 15 patients. Ozonated sodium chloride solution with ozone concentration of 3-4 µg/ml and drugs improving microcirculation were injected into the catheterised artery. At the same time, the author noted a positive effect, concluded that the pain syndrome disappeared, edema quickly decreased, the wound cleared and epithelialisation occurred. However, this method is not so easy to use in the treatment of patients with DFS, it is possible only in a clinic where all the conditions for performing this method are created, and specially trained personnel to serve this group of patients, but this method should be performed more effectively in the vascular department.

Along with anti-inflammatory therapy in patients with DFS complicated by purulent-necrotic process, it is necessary to carry out treatment aimed at improving hemodynamics of leg tissues, increasing tissue oxygen saturation and increasing immunological reactivity, which is sharply suppressed in DM and requires infusion therapy to eliminate intoxication. Only such a complex of measures prevents the progression of the process and the occurrence of sepsis (A. I. Brombin et al., 2001; M. F. Kalashnikova et al., 2010; P. S. Markevich et al., 2010; I. N. Pasechnik et al., 2016; N. Singh et al., 2005).

The works of Kuzin M. I. and Kostyuchenok B. M. (2012), the main provisions in the treatment of purulent wounds of various genesis have not lost their essence and are now supplemented only by new data.

Other researchers studied the effectiveness of sequential use of ultrasound cavitation (UDC) and bioplastic material “Collost” in 133 patients with purulent-necrotic complications of diabetic foot syndrome (DFS). Researchers concluded that the application of ultrasound with a working frequency F=25 kHz at an amplitude of 140/150 μm promotes rapid wound decontamination, and the sequential application of biomaterial Collost prevents secondary infection. The sequential application of bioplastic collagen material “Collost” and UDC promotes rapid closure of the defect, accelerating the appearance of granules and peripheral epithelization. Normalizes the course of the wound process in DFS.29

In the treatment of DFS with purulent-necrotic process, the researchers used ultrasonic cavitation with 0.2% solution of the drug Lavasept. The authors provided a rationale for the methodology and found that using this preparation there is a rapid reduction in bacterial fertilization, rapid wound cleansing and prevention of reinfection. This method contributes to the rapid transition of the first phase of the wound process to the second phase.30

Leontiev E. A. (2007) used hirudotherapy in the complex treatment of diabetic wounds, and Grigoryan A. Y. (2011) favored multicomponent ointments, Kabisova G. S. and other authors (2011) drainage sorbents.

Faglia E et al (2007) used subcutaneous injection of oxygen in the middle third of the tibia in the ischemic form of diabetic foot and indicated rapid wound healing, appearance of thickening and epithelization.

Usenbekov R. T. (2003) used hyperbaric oxygenation and 0.2% Curiosin solution locally in the treatment of DFS complicated by purulent process, which reduced the frequency of high amputations. However, Omorov R. A. and other authors (2006) stated that Curiosin is not effective in the treatment of purulent wounds in DFS patients at the first stage of the wound process, but good results were achieved at the second stage. But it was shown that curiosin was not widespread due to the high cost of the drug and the form of release, in fact one bottle is sufficient for only one dressing.

In local treatment of purulent wounds, antiseptics are also used, namely, dimexide in various concentrations, and the drug has a multicomponent action: anti-inflammatory, bactericidal, analgesic, immunocorrective, antioxidant, but in the literature we have not found information about its use in patients with DFS complicated by purulent-necrotic process.

Cochet S. (2002) used sulodexide and noted a positive effect on the wound process in patients with DFS.

Dibirov M. D., Hajimuradov R. I. (2019) introduced Remaxol into the complex of treatment of purulent complications and noted a positive effect on the course of the wound process.

Khalimov M. A. (2009) used NO - therapy in combination with local immunocorregulating drug myelopid in the treatment of purulent wounds.

In recent years, ozonized solutions have been used in the treatment of many diseases, especially purulent wounds. The bactericidal effect of ozone has been known for a long time, but its use was constrained by the lack of equipment, but with the development of ozonizers solutions have become widely used not only locally, but also intravenously and even intraarterially. Thus, Chakanov t. (2020) used intravenous administration of ozonated solution at a concentration of 3-4 mcg/ml in the treatment of DFS with purulent complications and noted a more favorable direction of the wound process compared to traditional methods.

У. M. Isaev et al, (2008) M. Mokhova, (2012) because of the accumulation of clinical material for wound healing using ozonized solutions revealed many components of their action: bactericidal, immunocorregative, antioxidant and ozonized solutions that contribute to increasing the sensitivity of microflora to antibiotics.

In local treatment of purulent wounds in patients with DM antiseptics, in particular 0.02% solution of decasan are used. Mikhalsky V. V. used the drug “Betadine” in the treatment of purulent wounds and noted that the wounds are quickly cleared. Lazarenko B. A. (2010) preferred to apply wound dressings on“ bio-herbs” and Tuysin S. R. (2010) used mixed dressings. Nabokin I. I. (2013), Koreyba K. A. et al. (2018), Riedel U. et al. (2020) states that in the treatment of post-traumatic stress disorder complicated by purulent-necrotic process, special dressings should also be used, which create optimal conditions for wound healing. The authors used AGNACEL AG dressings in the complex treatment of 20 patients with long-term non-healing wounds in patients with DFS, these dressings were used at the second stage of the wound process and noted early appearance of granulation and epithelization, as well as reduction of the wound surface.

Bebezov H. S. and other authors (2000) used sodium hypochloride solutions in the treatment of purulent diseases of soft tissues and noted rapid wound recovery, within 4-5 days from the beginning of treatment there was faster wound healing without detection of microflora. In order to prevent purulent-inflammatory complications in the treatment of neglected form of DFS, as well as in surgical patients against the background of diabetes mellitus, K. K. Aknazarov and other authors. (2006), Zholdoshbekov E. J. and Kultaev U. T. (2020) used sodium hypochlorite in a concentration of 0.06% intravenously 200 ml for 5-6 days and at the same time noted a faster improvement in the general condition, a decrease in pus discharge and more favorable wound healing compared to traditional treatment.

М. D. Dibirov et al, (2016); Y. Wrebel et al., (2013). say that in recent years there have been reports about the possibility of using collagen biomaterial in various diseases, in particular in DFS with purulent complications. In this regard, the works of B. S. Briskin and his authors (2009) deserve attention. The authors (2018) showed the results of using the local collagen biomaterial Collosta in the treatment of trophic ulcers in patients with DFS in the group of the most severe patients. In addition, the wound area, excreted culture was studied in dynamics. It was found that the use of colostomy collagen biomaterial promotes rapid reduction of the wound area (2 times compared to traditional treatment), does not cause side effects and leads to a reduction in the period of treatment in hospital and polyclinic.

In the treatment of purulent complications in DFS, physiotherapeutic methods are used mainly in combination with surgical and medications. Thus, Musaev A. I. et al. Authors. (2006), Derbenev V. A. (2010), Mnikhovich M. V. and Eromkin I. A. (2013) state that they applied laser irradiation of the wound area, which contributes to the rapid transition of the first phase of the wound process to the second.

According to the authors N. I. Troitskaya, K. G. Shapovalov, V. A. Mudrov, investigated the relationship of polymorphism of nitric oxide and endothelin - 1 synthase genes with the factors of regulation of vascular tone in diabetic foot syndrome. According to his findings, statistically significant differences in polymorphisms of the NAD1 gene in patients with uncomplicated diabetes mellitus and the development of diabetic foot were not found. Markers of uncomplicated endothelial dysfunction in 30 patients with diabetic foot syndrome and 30 patients with diabetes were also studied. No significant differences were found in endothelin-1 concentration in diabetic foot syndrome and uncomplicated diabetes.

In the complex treatment of DFS the method of gravitational therapy is also used, which is described by researchers N.N. Chur, M.V. Shkoda, V.V. Kondratenko, S.N. Chur. These scientists applied the method of gravitational therapy to 35 patients in combination with traditional methods of treatment and concluded that the appointment of gravitational therapy in the amount of 10 procedures reliably improves microcirculation parameters.

Foreign researchers describe the best results of using bioengineered skin substitutes (“Dermagraft”, “AlloDerm”, “Apligraf”) for the treatment of chronic wounds.31,32,33,34,35,36

As an equivalent, Russian authors use a similar product - “dermal equivalent” (DE) (Research Institute of Cytology, Russian Academy of Sciences, St. Petersburg, RF), consisting of allogeneic fibroblasts surrounded by collagen gel, which proved to be effective in the treatment of extensive burns and trophic ulcers of venous etiology.37,38,39

The use of DE in patients with DFS at the granulation stage stimulates the treatment processes and accelerates the epithelization rate compared to standard treatment of the neuropathic form.40

The use of thioctic acid, one of the supplements to the standard treatment of DFS, has also been studied. according to Dr. Prof. S. N. Styazhkin et al, In the study conducted, 184 patients with diabetes and diabetic foot syndrome were selected who were inpatients at the First Republican Clinical Hospital from 2016 to 2021. As a result of this study, these researchers concluded that adding thioctic acid to standard therapy has a positive effect on outcomes in patients with diabetic foot syndrome. The use of thioctic acid improves laboratory values and healing of ulcerative defects. In addition, its use results in fewer days of hospitalization and foot amputation.

**Conclusion:** Summarizing the literature review, analyzing the results of domestic and foreign literature, we note that scientific research on this topic has continued in recent years.

In general, modern methods of diabetic foot treatment represent a multilevel and individualized therapy aimed at improving wound healing, fighting infections and preserving limb function. The combined use of various techniques including surgical, drug, physiotherapy and novel approaches such as vacuum therapy and biomaterials significantly improves treatment outcomes and quality of life for patients.

This emphasizes the need to study new aspects of treatment and improve surgical tactics in patients with diabetic foot syndrome. Therefore, the study of this issue remains relevant.

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