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Neuropathic Ulcers in Diabetic Foot Syndrome: Dead End or New Horizons

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Abstract Neuropathic ulcers in diabetic foot syndrome remain one of the leading causes of disability and amputations in patients with diabetes mellitus. Despite the progress in treatment, the high rate of recurrence and chronicity of ulcers indicate persistent pathogenetic mechanisms that are not sufficiently addressed by standard therapy. This overview considers key aspects of the pathogenesis of neuropathic ulcers, clinical features of their course and modern approaches to diagnosis and treatment. Special attention is given to unresolved issues including the phenomenon of sterile inflammation, the scarcity of peripheral nerve regeneration techniques, and problems of healing stability. Special attention is given to unresolved issues, including the phenomenon of sterile inflammation, the scarcity of peripheral nerve regeneration techniques, and problems of healing stability. Promising therapeutic areas such as regenerative technologies, cellular platforms, gene therapy, the use of artificial intelligence and remote foot monitoring are highlighted. The pathways from a symptomatic treatment model to a comprehensive regenerative strategy are discussed.

Keywords Neuropathic ulcer, Diabetic foot syndrome, Neuropathy, Regenerative medicine, Artificial intelligence in medicine

1. Introduction

Diabetic foot syndrome (DFS) remains one of the most severe and socio-economically significant complications of diabetes mellitus, leading to disability, reduction in quality of life and increased mortality in patients. According to a recent global review, more than 19-34% of patients with diabetes mellitus experience foot ulcers during their lifetime, and 40-70% of cases require hospitalization while amputation rates remain extremely high [1]. Neuropathic ulcers are the most prevalent among the various forms of diabetic foot syndrome (DFS), defining the so-called “silent cascade” of progressive tissue destruction without obvious pain symptoms.

Neuropathic ulcer is not as much a local skin defect as a clinical manifestation of deep-lying pathological processes: sensory, motor and autonomic neuropathy, microcirculatory disorders and changes in the immune response. Recent studies confirm that chronic low-intensity inflammation and oxidative stress are central mechanisms for the development of neuropathic ulcers even in the absence of significant ischemia [2]. Thus, a neuropathic ulcer is more of an indicator of systemic failure rather than a purely local injury.

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Standardized treatment protocols including limb offloading, local ulcer treatment, and glycemic control demonstrate moderate efficacy, with complete healing achieved in 50-60% of patients within 12-20 weeks of therapy [3]. Nevertheless, the recurrence rate of neuropathic ulcers reaches 40% in the first year after healing and more than 60% within three years, indicating persistent pathogenetic factors not addressed by standard approaches.

The fact that even after complete healing of the ulcer, a significant proportion of patients retain a high risk of re-injury due to irreversible changes in the biomechanics of the foot, deterioration of tactile sensitivity and lack of full regeneration of peripheral nerves is extremely alarming[4]. These findings prompt a rethinking of traditional ideas about the goals of therapy for neuropathic ulcers, shifting the focus from wound healing to restoration of function and prevention of recurrence.

Current research indicates the need to integrate new technologies into the management strategy of patients with neuropathic ulcers. Biological dressings, nerve growth factors, methods of stimulating angiogenesis and neuroregeneration, the use of wearable pressure sensors for risk monitoring - all of these offer opportunities to overcome the current “deadlock” [5]. However, widespread clinical validation and standardization of these methods is still a challenge for the immediate future.

In this context, the question naturally arises: is the current state of treatment of neuropathic ulcers in diabetic foot syndrome a reflection of the deadlock of scientific and clinical efforts, or are we on the threshold of new horizons that will be opened due to the development of technology and a deeper understanding of the pathogenesis of the process? The answer to this question requires not only an analysis of current data, but also a sober assessment of unresolved issues, which is the purpose of this review.

2. Basics

Pathogenesis of neuropathic ulcers in diabetic foot syndrome

The development of neuropathic ulcers in patients with diabetes mellitus is a complex multistage process, which is based on the lesion of peripheral nerves of different caliber and functional purpose. Diabetic neuropathy occurs under the conditions of chronic hyperglycemia, contributing to the accumulation of glycation end products (AGEs), activation of the polyol pathway of metabolism and oxidative stress, which ultimately leads to impaired axonal transport, demyelination and death of nerve fibers [6].

Three components of diabetic neuropathy play a key role in ulcer formation: sensory, motor and autonomic. Sensory neuropathy leads to loss of pain sensitivity, which contributes to the development of microtrauma unnoticed by the patient. Motor neuropathy causes a disturbance in the tone and balance of the muscles of the foot, leading to the formation of pathologic pressure points and deformities (e.g., clawed toes) that contribute to localized overloading of the skin. Autonomic neuropathy impairs the function of sweat glands, leading to dry skin, cracking and impaired tissue trophism [7].

Microtraumatization occurring under conditions of loss of pain protection and biomechanical changes triggers processes of chronic damage to skin and subcutaneous tissues. Disruption of the regenerative capacity of keratinocytes and fibroblasts on the background of hyperglycemia prevents adequate healing of even minimal skin defects. Moreover, diabetes is associated with dysfunction of skin stem cells and decreased expression of growth factors necessary for tissue repair [8].

One of the central mechanisms of tissue damage in neuropathic ulcers is low-grade inflammation. Chronic metabolic stress activates nuclear factor κB (NF-κB), promoting the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and matrix metalloproteinases that degrade the extracellular matrix [9]. Oxidative stress induced by hyperglycemia exacerbates inflammation by disrupting the balance between the production of reactive oxygen species and antioxidant defense systems.

Prospective studies are focusing on exploring neuroregenerative approaches in the treatment of neuropathic ulcers, including the use of nerve tissue growth factors (NGF), mesenchymal stem cells, and gene therapy to restore normal skin innervation [10].

However, the introduction of these technologies into routine practice requires further clinical studies.

Thus, neuropathic ulcers should be considered as the result of a complex interaction of neuronal, vascular and immune disorders against the background of diabetes mellitus. Despite significant progress in understanding the key pathogenetic mechanisms, the role of microbiota, individual sensitivity to damage and criteria for assessing successful regeneration remain unresolved, which determines the directions of further research.

Clinical features and diagnosis of neuropathic ulcers

The clinical picture of neuropathic ulcers in diabetic foot syndrome has a number of characteristic features that determine the diagnosis at its early stages. For neuropathic ulcers is typical painless course on the background of pronounced tissue damage, which is associated with the loss of pain and temperature sensitivity. Most often ulcers are localized on the sole surface of the foot, in the area of metatarsophalangeal joints, fingertips, and in the interfinger spaces [11]. Ulcers have clear boundaries, dense hyperkeratotic edges and are often accompanied by calluses indicating chronic overloading.

Differential diagnosis of neuropathic ulcers with ischemic and neuroischemic lesions is crucial for the choice of therapeutic tactics. In contrast to ischemic ulcers, neuropathic wounds are located mainly in places of maximum pressure, and the skin around them, as a rule, remains warm and pink due to the preserved blood supply. Cold, pale skin and ulcers on the lateral surfaces of the foot or heel are observed in ischemic ulcers, which reflects impaired arterial blood supply [12].

The diagnosis of diabetic neuropathy is based on the use of simple clinical tests validated for general practice. The most common is the 10-gram Semmes-Weinstein monofilament test to detect loss of protective sensitivity. Vibration sensitivity is assessed using a 128 Hz tuning foramen or a biothesiometer. Additional tests include temperature and pain sensitivity, as well as assessment of tendon reflexes [13].

Instrumental methods allow to clarify the degree of neuropathy and the state of the vascular channel. Ankle-brachial pressure index (ABI) is the standard for assessment of macrocirculation, but its informative value is reduced in arterial mediocalcinosis. In such cases, transcutaneous measurement of partial pressure of oxygen ($TcPO_2$) is preferred. Electroneuromyography (ENMG) allows an objective assessment of the impulse conduction velocity along motor and sensitive fibers and reveals the degree of axonal or demyelinating lesions [14].

The diagnosis of subclinical neuropathy and scant symptomatic ulcers in elderly patients or those with cognitive impairment is particularly challenging. In these cases, classic symptoms may be obliterated, and the detection of neuropathy requires a more comprehensive multidisciplinary approach, including neuropsychological evaluation and advanced sensory tests [15].

A promising area of diagnostic development is the introduction of wearable sensors for continuous monitoring

of temperature and pressure on the surface of the foot, which allows the identification of risk areas before clinical symptoms appear. Thermography and artificial intelligence technologies also demonstrate high sensitivity in the early detection of changes preceding ulcer formation [16].

Principles of treatment of neuropathic ulcers: classical and innovative approaches

The treatment of neuropathic ulcers in diabetic foot syndrome requires a systematic approach aimed at achieving three main goals: complete closure of the wound defect, prevention of tissue infection and reduction of the risk of recurrence. Despite significant progress in understanding the pathogenesis, the basic principles of therapy remain unchanged and include complex correction of metabolic disorders, unloading of the affected limb and optimization of wound care [17].

Offloading the foot is recognized as the key to successful healing of neuropathic ulcers. The use of Total Contact Cast (TCC) immobilization, which allows even pressure distribution and minimizes microtrauma, has the greatest evidence base [18]. However, in real clinical practice, the use of removable cast walkers is widespread, although their effectiveness is lower due to insufficient patient adherence.

Local therapy of neuropathic ulcers is based on the principles of maintaining a moist wound environment, which helps to accelerate epithelialization and reduce the risk of infection. The use of modern atraumatic dressings, hydrogels, polyurethane foam coatings allows to create optimal conditions for tissue repair [19].

Infectious complications remain one of the predominant causes of progression of neuropathic ulcers and amputations. Antibiotic therapy should be based on the results of microbiologic examination and clinical assessment of the degree of infection. However, routine prophylactic administration of antibiotics in uninfected neuropathic ulcers is not recommended [20].

Glycemic control remains fundamental to effective ulcer healing. Meta-analyses show that achieving target HbA1c levels improves wound care outcomes and reduces the risk of infectious complications [21].

Modern biological bandages and skin substitutes with the inclusion of growth factors represent a promising direction of therapy of neuropathic ulcers. The use of recombinant platelet-derived growth factor (rhPDGF) and epidermal growth factor (EGF) promotes the stimulation of fibroblast and keratinocyte migration [22].

Of particular interest is the study of the possibilities of neural regeneration therapy in the treatment of neuropathic ulcers. Experimental data suggest that local injection of nerve tissue growth factors (NGF, IGF-1) can contribute to the recovery of sensory innervation of the skin and accelerate healing [23].

Stem cell therapy offers a new direction in regenerative medicine. Primary clinical studies show that the administration of mesenchymal stem cells (MSC) can improve angiogenesis, accelerate ulcer closure and promote tissue repair [24].

Vacuum-assisted wound care (VAC) has become widespread due to its ability to stimulate tissue granulation, remove exudate, and reduce bacterial load. Meta-analysis data confirm that VAC therapy accelerates the healing of neuropathic ulcers compared to traditional dressings [25].

Regenerative technologies, including 3D printing of biomaterial-based skin substitutes, open new perspectives in the treatment of complex chronic ulcers. Printing of skin constructs containing fibroblasts and keratinocytes allows individualizing treatment, reducing wound healing time [26]. Telemedicine and wearable devices are becoming important tools for monitoring foot conditions, especially in settings with limited access to specialized care. Remote monitoring of temperature and pressure on the feet of high-risk patients allows timely detection of podiatric conditions and reduces hospitalization rates [28].

Artificial intelligence and machine learning are increasingly used in predicting the risk of ulcer development and modeling treatment outcomes. Wound image analysis systems allow to automatically assess the dynamics of healing, predict the probability of complications and timely adjust the therapy tactics [27].

Problematic issues and unresolved aspects of therapy of neuropathic ulcers

Despite significant advancements in the treatment of neuropathic ulcers, their recurrence rate remains unacceptably high. Studies show that up to 40% of patients experience ulcer recurrence within the first year after healing, and within three years this figure exceeds 60% [29]. These data indicate that classical methods of ulcer treatment do not solve the fundamental problems of pathogenesis that contribute to their chronicization.

The problem of insufficient effectiveness of foot unloading remains one of the key problems in clinical practice. Despite the proven efficacy of TCC, patient adherence to wearing fixed devices remains low due to discomfort, risk of falls and restricted mobility [30]. This leads to increased mechanical stress on the foot tissues and an increased risk of recurrence.

A major limitation of current approaches is the inability to effectively treat diabetic neuropathy as the underlying cause of ulcer formation. Although improved glycemic control slows the progression of neuropathy, it does not reverse it. Currently, there are no registered pharmacologic agents capable of regenerating peripheral nerves in the setting of chronic diabetes [31].

The absence of standardized criteria for assessing peripheral nerve regeneration in clinical trials significantly complicates the interpretation of the results of new therapeutic approaches. Most studies are limited to subjective assessment of sensitivity or the use of surrogate markers, which reduces the level of evidence and hampers the widespread implementation of new technologies [32].

Another unresolved problem is the phenomenon of "sterile inflammation" in ulcers without signs of clinical infection. Often, antibiotics are empirically prescribed at the slightest suspicion of infection, which increases the risk of antibiotic-

resistant microflora formation [33]. New biomarkers are needed to differentiate inflammation caused by tissue trauma from actual infection.

Innovative technologies such as cell therapies, remote monitoring systems and artificial intelligence are showing encouraging results in research. However, their implementation into routine practice is hampered by high costs, lack of safety standards, regulatory barriers, and the need to train medical personnel [34].

The lack of a single criterion for treatment success remains a serious obstacle in interpreting the results of studies. Most studies focus on the time of ulcer healing, while the issues of foot function recovery, biomechanics, and patient's quality of life are often ignored [35].

Ultimately, successful treatment of neuropathic ulcers requires a multidisciplinary approach involving endocrinologists, surgeons, orthopedists, rehabilitation specialists, and psychologists. However, in practice, this approach is rarely implemented due to organizational difficulties, shortage of specialists, and lack of clear interdisciplinary protocols [36].

Promising areas of research and therapy for neuropathic ulcers

The development of methods for stimulating nerve regeneration is one of the most promising areas in the treatment of neuropathic ulcers. The application of growth factors such as nerve growth factor (NGF), insulin-like growth factor-1 (IGF-1), and brain-derived neurotrophic factor (BDNF) can activate the processes of remyelination and axonal growth, which theoretically can restore skin sensitivity and prevent microtrauma [37]. However, clinical trials are still in the early stages, and safety issues remain open.

Stem cell therapy opens new horizons for regenerative medicine. Mesenchymal stem cells (MSCs) demonstrate the ability to secrete growth factors, stimulate angiogenesis and modulate inflammation. Induced pluripotent stem cells (iPSCs) are considered as a source of autologous cellular material for repairing damaged tissues without the risk of immunologic rejection [38].

Gene therapy is also growing in popularity as a potential method of stimulating the processes of angiogenesis and regeneration of nerve components. The use of vectors for the expression of VEGF, NGF and other growth factors directly in the affected tissues is promising. Preliminary clinical studies show the possibility of improving tissue perfusion and stimulation of nerve repair [39].

The use of new biomaterials and 3D printing technologies of skin analogues allows the creation of individualized skin grafts containing the patient's cells. These constructs provide structural support for healing and can be supplemented with growth factors or stem cells to enhance regenerative processes [40].

Artificial intelligence (AI) and machine learning are becoming powerful tools to predict ulcer formation, automatically assess healing dynamics, and individualize treatment tactics. Algorithms based on image analysis can predict the risk of complications with high accuracy long before clinical symptoms [41].

Remote foot monitoring technologies, such as portable sensors for pressure, temperature, and humidity, are already undergoing clinical validation. Devices integrated into shoes or insoles can detect changes in real time before ulcer formation and thus significantly reduce the risk of serious complications [42].

Immunotherapy and targeted modulation of chronic inflammation are also considered as promising approaches. Blockade of proinflammatory cytokines, such as TNF-α or IL-6, or stimulation of regulatory pathways can reduce inflammatory activity in the ulcer area and accelerate healing processes [43].

The integration of multidisciplinary management models that include not only surgical and metabolic treatment, but also psychological support, rehabilitation, and educational programs for patients is essential for successful long-term disease control [44].

3. Conclusions

Neuropathic ulcers in diabetic foot syndrome remain one of the most challenging clinical problems of modern medicine. The high frequency of their occurrence, recurrences and complications emphasizes that traditional methods of treatment, despite the successes achieved, have not yet solved the fundamental problems underlying ulcer formation. Mechanisms of neuropathy, chronic sterile inflammation, and impaired regeneration continue to play a leading role in the chronicization of the process, and the limited options of current therapies indicate the current “deadlock” in the struggle for full recovery.

Nevertheless, new horizons are becoming more and more clearly visible. Research in neuroregeneration, gene and cell therapy, the development of biomaterials, and the introduction of artificial intelligence and remote monitoring of the foot are opening up qualitatively different possibilities for the treatment and prevention of neuropathic ulcers. Personalized approaches based on the integration of multidisciplinary efforts offer the hope of improving both wound healing and sustained functional recovery.

It is important to realize that overcoming the existing barriers will require not only technological developments, but also a revision of the conceptual framework of patient management: from the “heal the wound” model to the “restore and preserve function” model. In this context, each new study, each new clinical innovation becomes not only a step forward, but also a contribution to reconsidering the very essence of medical care for patients with diabetic neuropathy.

Thus, neuropathic ulcer in diabetic foot syndrome is not the dead end, but a challenge that requires complex solutions and interdisciplinary collaboration. And it is on the horizon of the synthesis of clinical, technological and biomedical achievements that we can see a real prospect of changing the fate of millions of patients around the world.

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