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DIABETIC NEUROPATHY: INNOVATIVE APPROACHES TO DIAGNOSIS AND TREATMENT AUTHORS

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SUMMARY
Diabetic neuropathy is one of the most severe complications of diabetes mellitus, significantly impairing patients' quality of life. This article presents current approaches to the diagnosis and treatment of this condition, including the application of innovative technologies such as gene and cell therapy, nanotechnology, and artificial intelligence. Special emphasis is placed on prevention and the interdisciplinary approach aimed at improving patient outcomes.

KEYWORDS: *diabetic neuropathy, diagnosis, treatment, prevention, gene therapy, cell therapy, nanotechnology, artificial intelligence.*

CONFLICT OF INTEREST. The authors declare no conflict of interest.

ДИАБЕТИЧЕСКАЯ НЕЙРОПАТИЯ: НОВЫЕ ПОДХОДЫ К ДИАГНОСТИКЕ И ЛЕЧЕНИЮ

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РЕЗЮМЕ
Диабетическая нейропатия – одно из наиболее тяжёлых осложнений сахарного диабета, существенно ухудшающее качество жизни пациентов. В статье представлены современные подходы к диагностике и лечению этого состояния, включая использование инновационных технологий, таких как генная и клеточная терапия, нанотехнологии и искусственный интеллект. Особое внимание уделено профилактике и междисциплинарному подходу, направленному на улучшение прогнозов пациентов.

КЛЮЧЕВЫЕ СЛОВА: *диабетическая нейропатия, диагностика, лечение, профилактика, генная терапия, клеточная терапия, нанотехнологии, искусственный интеллект.*

КОНФЛИКТ ИНТЕРЕСОВ. *Авторы заявляют об отсутствии конфликта интересов.*

Introduction

Diabetic neuropathy (DN) is one of the most common and severe complications of diabetes mellitus (DM). It affects approximately 50% of patients with long-standing DM and may develop in both type 1 and type 2 diabetes. The diversity of clinical manifestations, including sensory, motor, and autonomic disturbances, makes DN not only a medical but also a social problem that significantly impairs patients' quality of life [1, 2].

According to the World Health Organization (WHO), about 422 million people worldwide are affected by diabetes, and this number continues to rise. Considering that the risk of developing DN correlates with the duration of the disease and the level of glycemic control, the problem of early diagnosis and effective treatment becomes especially urgent. Diabetic neuropathy is associated with increased disability rates, decreased work capacity, and a growing financial burden on healthcare systems, particularly in developing countries.

Existing diagnostic methods often rely on subjective assessment of symptoms and do not always allow for detection of the disease at early stages. As a result, interest is growing in new instrumental and molecular techniques, including the use of biomarkers and modern imaging technologies. Significant changes are also taking place in the field of treatment: new pharmacological agents and innovative approaches are emerging, aimed at neural tissue repair and reduction of pain symptoms [3–6].

The purpose of this article is to provide a comprehensive overview of current approaches to the diagnosis and treatment of diabetic neuropathy, including promising methods that may change patient management in the near future. Attention will be paid to pathogenetic aspects, innovative technologies, and preventive measures aimed at reducing the prevalence of this complication.

Etiopathogenesis of Diabetic Neuropathy

Diabetic neuropathy (DN) has a complex and multifactorial pathogenesis based on metabolic, vascular, and immune mechanisms. Chronic hyperglycemia is considered the key trigger initiating a cascade of pathological changes in nerve tissue. It activates several processes, including the polyol metabolic pathway, which leads to the accumulation of sorbitol and a decrease in the level of myo-inositol – both essential for the normal functioning of nerve fibers. As a result, electrolyte balance and ion transport across neuronal membranes are disrupted, further exacerbating the pathological changes. In addition, chronic hyperglycemia contributes to the formation of advanced glycation end-products (AGEs), which trigger inflammatory reactions and enhance oxidative stress, exerting a toxic effect on nerve tissue [7–9].

The Role of Oxidative Stress and Inflammation

One of the central mechanisms in the pathogenesis of diabetic neuropathy is oxidative stress, initiated by the excessive production of reactive oxygen species (ROS). These highly reactive molecules cause damage to cell membranes through lipid peroxidation and also modify protein and DNA structures, thereby initiating apoptotic signaling cascades in neurons. Such changes lead to the activation of inflammatory pathways, including the synthesis of proinflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α). These mediators exacerbate neural damage, increase vascular permeability, and promote hypoxia progression. Thus, oxidative stress not only induces primary axonal injury but also creates a chronic environment that impairs the regeneration of nerve fibers [10].

Microvascular Ischemia and Hypoxia

Diabetic microangiopathy, affecting the blood vessels that supply nerves, leads to ischemia and hypoxia of the nerve fibers. The persistent reduction in oxygen levels directly damages nerve endings and worsens the pathological process. This impairment in nutrient and oxygen transport to nerve cells creates a foundation for further progression of neuropathy [11].

Pathogenetic Classification

Diabetic neuropathy is classified into several forms depending on clinical presentation.

- Sensory neuropathy is characterized by altered sensation, including paresthesia and pain. These manifestations are often underestimated by patients in the early stages.
- Motor neuropathy presents with muscle weakness and atrophy, significantly reducing patients' physical activity and overall condition.
- Autonomic neuropathy affects internal organ function, causing disturbances such as orthostatic hypotension, gastroparesis, and erectile dysfunction.

Modern understanding of the pathogenesis of diabetic neuropathy opens new perspectives for its diagnosis and treatment. The following section will examine innovative approaches to detecting this condition.

Current Approaches to Diagnosis

Modern diagnostic strategies for diabetic neuropathy are based on the integration of clinical, instrumental, and molecular approaches, which significantly enhance the accuracy of early detection.

Instrumental Methods

One of the key instrumental techniques is electromyography (EMG), which evaluates the functional state of peripheral nerves and detects alterations in nerve conduction velocity. However, despite its widespread use, this method requires highly qualified medical personnel and access to specialized equipment.

Another important diagnostic tool is skin biopsy, employed to assess the density of small nerve fibers and identify their degeneration. This method provides unique insights into the condition of neural structures that cannot be obtained through other diagnostic modalities.

Additionally, ultrasound and magnetic resonance neurography (MRN) enable visualization of peripheral nerve structures, detecting pathological changes that may remain unnoticed with standard diagnostic methods [12, 13].

Clinical Tests

Clinical tests remain an essential component of DN diagnosis. The most commonly used include:

- Vibration perception test using a tuning fork – a convenient method for rapid, non-invasive screening of sensory disturbances, particularly in early disease stages.
- Semmes – Weinstein monofilament test – evaluates tactile sensitivity. Its simplicity and accessibility make it a valuable tool in clinical practice.
- Quality of life questionnaires, such as DN4 (Douleur Neuropathique 4), aid in assessing the presence and severity of pain syndrome, as well as in planning subsequent treatment strategies.

Liquid Biopsy

Liquid biopsy is an emerging diagnostic approach based on the analysis of biological fluids for the identification of specific biomarkers. For instance, neurofilaments, glycoproteins, and proinflammatory cytokines can be used to evaluate the extent of nerve tissue damage and the activity of inflammatory processes. These markers not only support disease diagnosis but also enable monitoring of disease progression and treatment efficacy [14, 15].

New Approaches to Treatment

Pharmacological Therapy

Modern pharmacological agents used in the treatment of diabetic neuropathy aim to target the underlying pathogenic mechanisms and alleviate symptoms. Among them:

- Antioxidants: Alpha-lipoic acid has demonstrated efficacy in randomized clinical trials, showing its ability to reduce sensory symptoms and slow the progression of neuropathy [16].
- Metabolic agents: Polyol pathway inhibitors, such as epalrestat and isodibutine, reduce sorbitol accumulation in nerve tissue, thereby limiting neuronal damage [17].

Neuroprotective Agents

To promote nerve repair, the following are actively utilized:

- Agents that stimulate nerve fiber growth, such as cerebrolysin, which show beneficial effects on regeneration and function of the peripheral nervous system.
- Poly(ADP-ribose) polymerase (PARP) inhibitors, which help reduce oxidative stress and prevent DNA damage, playing a role in halting neuropathy progression.

Pain Management

Pain is one of the cardinal symptoms of diabetic neuropathy. Management strategies include:

- First-line drugs: Duloxetine and amitriptyline, which reduce pain intensity by acting centrally on neuropathic mechanisms.
- Antiepileptic agents: Gabapentin and pregabalin, which are the standard pharmacologic treatments for neuropathic pain.
- Innovative therapies: Botulinum toxin for localized pain relief and cannabinoids, which have shown efficacy in chronic pain syndromes.

Therapeutic Prospects

Gene Therapy

Recent advances in genetic engineering have opened new horizons for diabetic neuropathy treatment:

- Use of viral vectors to deliver growth factors such as NGF and BDNF aids in regenerating damaged nerve fibers. These factors are key in neuronal regeneration and intercellular communication, which are essential for restoring peripheral nervous system function [18].
- CRISPR-Cas9 technology allows gene modification involved in neuropathy pathogenesis, facilitating both prevention and treatment. For example, research explores correcting mutations that increase neuronal sensitivity to hyperglycemia [19].
- Gene therapy is also being investigated to improve microcirculation in nerve tissue by upregulating genes responsible for angiogenesis, potentially reducing ischemic injury.

Cell Therapy

Cell-based technologies offer novel options for nerve tissue regeneration:

- Mesenchymal stem cells (MSCs) possess regenerative potential and support remyelination of damaged axons. Their secretion of neurotrophic factors makes them a promising tool for DN treatment. Moreover, MSCs can suppress inflammatory responses exacerbating nerve damage.
- Schwann cell transplantation is being studied as a method to enhance nerve regeneration. These cells restore the myelin sheath and create favorable conditions for axonal growth.
- Combined approaches, integrating cellular therapies with biomaterials such as hydrogels, are also under investigation to improve transplantation efficacy and promote sustained tissue repair.

Nanotechnology

Nanotechnology provides unique solutions for targeted drug delivery:

- Nanoparticles enable site-specific delivery of antioxidants and anti-inflammatory agents. Due to their small size, they can reach otherwise inaccessible regions of nerve tissue, minimizing systemic side effects.
- Liposomes offer sustained drug release, reducing dosing frequency and enhancing treatment effectiveness. They can also carry combination therapies, improving overall efficacy.
- Magnetic nanoparticles, guided by external magnetic fields, allow localized drug delivery, minimizing collateral tissue damage.

The Role of Prevention in DN Management

Preventive strategies are crucial for reducing the prevalence of diabetic neuropathy:

- Maintaining target glycemic levels in accordance with modern clinical guidelines remains the cornerstone of neuropathy prevention. This includes the use of real-time glucose monitoring systems, allowing patients to promptly adjust glucose levels [20].
- A healthy lifestyle, incorporating regular physical activity, a balanced diet, and avoidance of harmful habits, reduces the risk of complications. For instance, aerobic exercise improves microcirculation and reduces inflammation [21].
- Screening programs facilitate early detection and timely intervention before irreversible changes develop. Mobile clinic-based initiatives have proven effective in rural settings where access to healthcare is limited [22].

Clinical Trials and Current Challenges

Clinical trials dedicated to diabetic neuropathy aim to enhance understanding of its pathogenesis, develop novel diagnostic tools, and implement innovative treatment strategies. In recent years, several large-scale studies have clarified the efficacy of various therapeutic approaches. For example, research has shown that alpha-lipoic acid and polyol pathway inhibitors significantly reduce neuropathic symptoms, including pain and sensory dysfunction.

Other studies have focused on evaluating the effectiveness of combination therapies. The synergistic effect of antioxidants with neuroprotective agents such as cerebrolysin promotes nerve tissue regeneration. Furthermore, clinical trials are investigating the utility of novel biomarkers that may aid early diagnosis and serve as indicators of therapeutic success [23, 24].

However, current diagnostic and treatment methods have limitations. Tools such as biomarkers and skin biopsies require specialized equipment and trained personnel, restricting their use in primary care settings. Moreover, pharmacological treatments often have side effects and do not ensure full neural restoration. For example, while duloxetine reduces pain, it does not address the core pathogenic mechanisms of neuropathy.

The economic burden of diabetic neuropathy also poses a significant challenge. The high cost of medications and diagnostics renders them inaccessible for many patients, particularly in developing countries. The lack of insurance coverage for modern diagnostic and therapeutic options further exacerbates the problem. These issues highlight the need to develop cost-effective diagnostic and therapeutic methods accessible to a broader patient population. Mass screening programs for early-stage neuropathy represent a promising approach to reducing the cost of late-stage treatment.

Conclusion

Diabetic neuropathy remains one of the most complex challenges in modern medicine, requiring a multifaceted approach. The development of innovative diagnostic and treatment strategies is critical for improving patients' quality of life and minimizing the socioeconomic impact of this condition. Promising technologies, including gene and cell therapies, nanotechnology, and personalized medicine, offer unique opportunities for individualized treatment – especially important given the chronic nature of diabetic neuropathy.

Preventive measures warrant special attention, as early intervention can significantly delay disease progression. For example, improving glycemic control and implementing new monitoring tools – such as wearable devices for peripheral nerve assessment – can markedly enhance preventive strategies. Furthermore, combining traditional methods with advanced technologies like artificial intelligence for patient data analysis opens avenues for developing personalized treatment plans tailored to individual needs.

The integration of interdisciplinary approaches, uniting expertise from endocrinology, neurology, and bioengineering, is essential for creating more effective therapeutic strategies. This collaboration may not only improve treatment outcomes but also lead to the establishment of new standards of care, alleviating the healthcare system's burden. Finally, the implementation of educational programs for healthcare professionals and patients will enhance awareness and adherence to treatment, ensuring broader success in combating diabetic neuropathy.

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