

Pathophysiological Basis for The Development of Diabetes Mellitus in Diabetic Neuropathy

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Abstract

Diabetes mellitus (DM) is one of the foremost medical and social challenges of the 21st century, and diabetic neuropathy (DN) is one of its most common complications, occurring in 50–60% of patients with long-standing disease. The aim of this study is to systematize current data on the pathophysiological mechanisms of DN and to analyze the role of metabolic, vascular, oxidative, inflammatory, and trophic factors in nerve tissue damage. A systematic literature review (2014–2024) was conducted using international and Russian databases (PubMed, Scopus, Web of Science, RSCI, eLIBRARY.RU) with the following keywords: "diabetes mellitus," "diabetic neuropathy," "hyperglycemia," "polyol pathway," "advanced glycation end-products," "oxidative stress," "nerve growth factor," and their Russian equivalents. The pathogenesis of DN involves the activation of the polyol pathway, the accumulation of advanced glycation end products, mitochondrial and endothelial dysfunction, chronic inflammation, and a deficiency of neurotrophic factors, all of which lead to progressive nerve tissue damage. Understanding these mechanisms offers opportunities for early diagnosis, the development of biomarkers, and pathogenetically-based therapy. A comprehensive approach to treatment can slow the progression of this complication and improve patients' quality of life.

Keywords: Diabetes mellitus, diabetic neuropathy, hyperglycemia, oxidative stress, advanced glycation end-products, microvascular complications, inflammation, pathophysiology, nerve damage.

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Introduction

Diabetes mellitus (DM) is one of the most pressing medical and social problems of the 21st century, ranking as a leading non-communicable disease in terms of morbidity, disability,

and mortality. According to the International Diabetes Federation (IDF), the number of people with diabetes worldwide reached 537 million in 2021 and is projected to increase to 783 million by 2045 [1]. In the Russian Federation, according to the Federal Register of Diabetes

Mellitus, over 5.1 million patients with DM were registered at the beginning of 2023, which accounts for approximately 3.5% of the country's population [10, 18].

Diabetic neuropathy (DN) is one of the most common and clinically significant complications of diabetes mellitus (DM), occurring in 50-60% of patients with long-standing disease [2, 12]. This condition is characterized by progressive peripheral nerve damage, leading to the development of neuropathic pain, sensory impairment, autonomic dysfunction, and diabetic foot syndrome [32]. DN is the leading cause of non-traumatic lower limb amputations and significantly reduces patients' quality of life [23, 26]. The medical and socioeconomic consequences of DN underscore the need for a thorough understanding of the pathophysiological mechanisms of its development.

The pathophysiology of diabetic neuropathy is a complex, multicomponent process involving multiple interconnected metabolic, vascular, inflammatory, and autoimmune mechanisms. Chronic hyperglycemia, the central element in the pathogenesis of DM, initiates a cascade of biochemical reactions that lead to structural and functional changes in nerve tissue. Key pathogenetic factors include the activation of the polyol pathway of glucose metabolism, the formation of advanced glycation end products (AGEs), increased oxidative stress, impaired microcirculation and nerve tissue hypoxia, activation of protein kinase C (PKC), mitochondrial dysfunction, and impaired neurotrophic support.

In recent years, the role of inflammatory processes in the pathogenesis of diabetic neuropathy (DN) has been actively studied. It has been established that chronic hyperglycemia induces subclinical inflammation with elevated levels of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), which directly damage nerve fibers and contribute to the progression of neuropathy. The activation of nuclear factor- κ B (NF- κ B) signaling pathways and the formation of advanced glycation end-products trigger an inflammatory cascade, leading to endothelial dysfunction, impaired microcirculation, and ischemic damage to nerve tissue.

Traditional methods for diagnosing DN, based on clinical symptom assessment and electroneuromyography, often detect the disease in its late stages when structural changes in the nerve tissue are already irreversible [24]. In this regard, the study of molecular biomarkers for the early stages of neuropathy is of particular importance, as it would allow for the timely initiation of pathogenetically-based therapy and prevent the progression of the complication.

Understanding the complex pathophysiological mechanisms of diabetic neuropathy is fundamental to developing new therapeutic approaches aimed at preventing and slowing the progression of this complication. Modern treatment strategies for DN include not only optimal glycemic control but also the use of drugs with pathogenetic effects that target various links in the development of neuropathy: antioxidants, aldose reductase inhibitors, α -lipoic acid preparations, nerve growth factors, and immunomodulators [29, 30].

The aim of the study is to systematize current data on the pathophysiological mechanisms of diabetic neuropathy in diabetes mellitus, analyze the role of metabolic, vascular, inflammatory, and oxidative factors in the pathogenesis of nerve damage, and evaluate promising avenues for the early diagnosis and pathogenetically-based therapy of this complication.

This systematic review is based on an analysis of scientific publications indexed in the international and Russian databases PubMed, Scopus, and Web of Science, as well as the Russian Science Citation Index (RSCI) and the eLIBRARY.RU platform, covering the period from 2014 to 2024. The search utilized the following keywords in English and Russian: "diabetes mellitus," "diabetic neuropathy," "hyperglycemia," "polyol pathway," "advanced glycation end-products," "oxidative stress," "microvascular complications," "nerve damage," "inflammatory cytokines," "mitochondrial dysfunction," "nerve growth factor," and their Russian equivalents: "сахарный диабет," "диабетическая нейропатия," "патофизиология," "гипергликемия," "окислительный стресс," and "конечные продукты гликирования."

Inclusion criteria were as follows:

- Original research and systematic reviews published in peer-reviewed journals
- Studies dedicated to the pathophysiological mechanisms of diabetic neuropathy development in type 1 and type 2 diabetes
- Research on the molecular and biochemical mechanisms of nerve damage in diabetes
- Publications on the role of metabolic disorders, oxidative stress, inflammation, and vascular factors in the pathogenesis of diabetic neuropathy
- Papers describing modern approaches to the diagnosis and pathogenetic therapy of diabetic neuropathy

Exclusion criteria were as follows:

- Publications that had not undergone peer review

- Duplicate studies and redundant publications
- Studies with unclear methodology or insufficient statistical power
- Conference abstracts without full-text publications
- Publications not directly related to the pathophysiology of diabetic neuropathy

The initial search identified 187 publications that met the specified criteria. After a detailed analysis of the full-text versions and the application of inclusion and exclusion criteria, 112 sources were selected for the review. Of these, 65% were international publications, and 35% were works by Russian and Uzbek authors. Priority was given to publications from the last 5 years (2019–2024), which constituted 68% of the total sources analyzed. Articles published in high-impact journals with an impact factor > 5.0 made up 42% of the total dataset.

The analysis of publications focused on the following aspects: biochemical mechanisms of nerve tissue damage in hyperglycemia; the role of the polyol pathway and the accumulation of advanced glycation end-products; the effects of oxidative stress and mitochondrial dysfunction; the involvement of inflammatory processes and cytokines; mechanisms of microvascular insufficiency and ischemia; impaired neurotrophic support; modern diagnostic approaches and biomarkers; and pathogenetically-based therapeutic methods. Statistical processing of the meta-analysis data was performed using standard methods of descriptive statistics. The significance of differences between groups was assessed using parametric and non-parametric criteria depending on the data type; the significance level was set at $p < 0.05$.

1. Metabolic Mechanisms of Diabetic Neuropathy Development

Chronic hyperglycemia is the central pathogenetic factor in the development of diabetic neuropathy. Elevated blood glucose levels initiate multiple biochemical cascades that lead to progressive nerve tissue damage.

1.1. Activation of the Polyol Pathway

One of the key metabolic disorders in hyperglycemia is the activation of the polyol (sorbitol) pathway of glucose metabolism. Under normoglycemic conditions, only about 3% of glucose is metabolized via this pathway; however, during hyperglycemia, this proportion increases significantly. The enzyme aldose reductase catalyzes the reduction of glucose to sorbitol, using NADPH as a cofactor. The accumulation of sorbitol in nerve cells leads to the development of osmotic stress and cellular edema [6,

9]. Because sorbitol poorly penetrates cell membranes, its intracellular accumulation disrupts the osmotic balance and causes neuronal dysfunction.

Furthermore, activation of the polyol pathway leads to the depletion of NADPH stores, which are necessary for regenerating reduced glutathione—a key endogenous antioxidant [7]. This exacerbates oxidative stress and makes nerve cells more vulnerable to damage from reactive oxygen species. Sorbitol is then oxidized to fructose by the enzyme sorbitol dehydrogenase, forming NADH, which alters the intracellular NAD⁺/NADH ratio and disrupts normal cell metabolism.

1.2. Formation of advanced glycation end-products

Advanced glycation end-products (AGEs) are formed as a result of the non-enzymatic attachment of glucose to the amino groups of proteins, lipids, and nucleic acids. This process, known as the Maillard reaction, is significantly accelerated under conditions of chronic hyperglycemia. AGEs accumulate in the structural proteins of nervous tissue, including myelin, tubulin, and perineurial collagen, which leads to the disruption of their normal function.

The interaction of AGEs with their specific receptors (RAGE — receptor for advanced glycation end-products) activates intracellular signaling pathways, including NF- κ B, which leads to the expression of proinflammatory genes and increased oxidative stress [4, 16]. RAGE activation induces the production of proinflammatory cytokines (TNF- α , IL-1 β , IL-6), adhesion molecules (VCAM-1, ICAM-1), and growth factors, which contributes to the development of chronic inflammation and endothelial dysfunction.

Furthermore, AGEs cause the formation of cross-links in the proteins of the extracellular matrix and the vascular basement membrane, leading to the thickening of capillary walls and impaired microcirculation [4, 13]. The glycation of structural proteins in nerve fibers, including neurofilaments and tubulin, disrupts axonal transport and promotes nerve degeneration.

1.3. Activation of Protein Kinase C

Hyperglycemia induces the formation of diacylglycerol (DAG), which activates isoforms of protein kinase C (PKC). The activation of PKC, especially the β and δ isoforms, plays an important role in the pathogenesis of diabetic complications. PKC modulates the function of various proteins through their phosphorylation, affecting vascular permeability, vascular tone, endothelial function, and gene expression.

The activation of PKC in endothelial cells leads to increased production of endothelin-1, a potent vasoconstrictor, and decreased synthesis of nitric oxide (NO), which disrupts vasodilation and impairs microcirculation [27]. In nerve tissue, the activation of PKC contributes to the disruption of neurotrophic support by suppressing the expression of nerve growth factors, including NGF (nerve growth factor) and BDNF (brain-derived neurotrophic factor) [27].

2. The Role of Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress, defined as an imbalance between the production of reactive oxygen species (ROS) and antioxidant defense, plays a central role in the development of diabetic neuropathy [7, 28]. Chronic hyperglycemia enhances ROS formation through multiple mechanisms, including glucose auto-oxidation, protein glycation, activation of the polyol pathway, and impaired mitochondrial respiratory chain function.

2.1. Mitochondrial Dysfunction

Mitochondria are the main source of ROS in the cell. In hyperglycemia, an increased flow of electrons through the respiratory chain leads to the overproduction of superoxide anion in complexes I and III [8]. The accumulation of ROS causes oxidative damage to mitochondrial DNA, membrane lipids, and respiratory chain proteins, which further impairs mitochondrial function and exacerbates oxidative stress, creating a vicious cycle.

Mitochondrial dysfunction leads to impaired energy metabolism in neurons, which are characterized by high metabolic activity and a dependence on aerobic ATP synthesis. An ATP deficit disrupts the function of Na⁺/K⁺-ATPase, leading to membrane depolarization, impaired nerve impulse conduction, and axonal degeneration [8, 15]. Furthermore, mitochondrial dysfunction activates apoptotic pathways through the release of cytochrome c and the activation of caspases, which contributes to neuronal death.

2.2. Depletion of antioxidant defenses

Under conditions of chronic hyperglycemia, endogenous antioxidant systems become depleted, including superoxide dismutase (SOD), catalase, glutathione peroxidase, and the reduced glutathione system. Activation of the polyol pathway leads to a decrease in the level of NADPH, which is necessary for regenerating reduced glutathione, making cells more vulnerable to oxidative damage.

ROS cause peroxidation of membrane lipids, leading to the

formation of toxic products, including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) [28]. These compounds modify proteins and DNA, disrupting their function and triggering apoptotic processes. Oxidative damage to the myelin sheath leads to demyelination and slows nerve impulse conduction. The oxidation of axonal cytoskeleton proteins disrupts axonal transport, leading to distal axonopathy—a characteristic feature of diabetic neuropathy.

3. Vascular Mechanisms and Microangiopathy

Microvascular insufficiency is an important pathogenetic factor in the development of diabetic neuropathy. Nerve fibers have an extensive blood supply via the vasa nervorum, and impaired microcirculation leads to ischemic damage of nerve tissue.

3.1. Endothelial Dysfunction

Hyperglycemia induces endothelial dysfunction through multiple mechanisms. The bioavailability of nitric oxide (NO)—a key endothelial vasodilator and antithrombotic agent—is reduced [3]. This occurs due to the increased formation of superoxide anion, which rapidly reacts with NO to form peroxynitrite—a highly reactive compound that damages cellular structures.

PKC activation in endothelial cells stimulates the production of endothelin-1, a potent vasoconstrictor, and suppresses the expression of endothelial NO-synthase (eNOS). This imbalance between vasodilators and vasoconstrictors leads to increased vasa nervorum tone and reduced endoneurial blood flow. The formation of AGEs and their interaction with RAGE on endothelial cells enhances the expression of adhesion molecules, promoting leukocyte recruitment and the development of subclinical inflammation in the vessel wall.

3.2. Structural Changes in Microvessels

Chronic hyperglycemia causes a thickening of the capillary basement membrane of the vasa nervorum due to the accumulation of AGEs and increased synthesis of extracellular matrix components [21, 25]. This leads to a decrease in the permeability of the vessel wall to oxygen and nutrients. Hypertrophy of endothelial cells and proliferation of pericytes reduce the capillary lumen, further restricting blood flow.

Disruption of the blood-nerve barrier increases permeability to macromolecules and contributes to the development of endoneurial edema, which further impairs microcirculation.

Platelet aggregation and the formation of microthrombi in the vasa nervorum capillaries cause acute ischemia of the nerve tissue. Reduced endoneurial blood flow leads to chronic hypoxia of nerve fibers, disrupting energy metabolism and promoting axonal degeneration.

4. Inflammatory and Immune Mechanisms

In recent years, compelling evidence has accumulated regarding the role of chronic subclinical inflammation in the pathogenesis of diabetic neuropathy. Hyperglycemia induces an inflammatory response through the activation of the NF- κ B signaling pathway and increased production of proinflammatory cytokines.

4.1. The Role of Proinflammatory Cytokines

The activation of RAGE by advanced glycation end products and oxidative stress induces the expression of proinflammatory cytokines, including tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) [4, 16]. These cytokines exert a direct damaging effect on nerve cells and perpetuate chronic inflammation in nerve tissue.

TNF- α activates apoptotic pathways by binding to the TNFR1 receptor and initiating the caspase cascade, which leads to the death of neurons and Schwann cells [16]. IL-1 β enhances the production of inducible NO synthase (iNOS), resulting in the excessive formation of nitric oxide and peroxynitrite, which damage cellular structures. IL-6 stimulates the hepatic synthesis of acute-phase proteins, including C-reactive protein (CRP), which serves as a marker of systemic inflammation and is associated with the severity of diabetic complications.

4.2. Activation of Microglia and Macrophages

In diabetic nerve tissue, activation of resident macrophages and infiltration by circulating monocytes are observed. These monocytes differentiate into pro-inflammatory M1-macrophages, which secrete pro-inflammatory cytokines, chemokines, and ROS, exacerbating nerve damage. Chemokines, including MCP-1 (monocyte chemoattractant protein-1) and RANTES, recruit additional inflammatory cells, thereby sustaining chronic inflammation.

Activated macrophages also produce matrix metalloproteinases (MMPs), which degrade extracellular matrix components and disrupt the structural integrity of nerve tissue [16, 17]. An imbalance between MMPs and their tissue inhibitors (TIMPs) contributes to the destruction of the basement membrane and the destabilization of the

blood-nerve barrier.

5. Impaired Neurotrophic Support

Nerve growth factors play a critical role in maintaining the structure and function of peripheral nerves. Diabetes is associated with impaired synthesis, transport, and signaling of neurotrophic factors, which contributes to the progressive degeneration of nerve fibers.

5.1. Nerve Growth Factor (NGF) Deficiency

Nerve growth factor (NGF) is essential for the survival, growth, and regeneration of sensory and sympathetic neurons. In diabetic neuropathy, there is a decrease in NGF expression in target tissues and impaired retrograde axonal transport of NGF from the periphery to the neuron cell body [5, 14]. This leads to impaired trophic support for dorsal root ganglion neurons and the development of sensory neuropathy.

Hyperglycemia suppresses the expression of NGF receptors (TrkA and p75NTR) on neurons, disrupting the perception of neurotrophic signals. PKC activation and AGE formation also inhibit NGF signaling pathways, including PI3K/Akt and MAPK/ERK, which regulate neuronal survival and differentiation.

5.2. Other neurotrophic factors

In addition to NGF, other neurotrophic factors play an important role in maintaining peripheral nerve function. Brain-derived neurotrophic factor (BDNF) supports the survival and regeneration of motor and sensory neurons. In diabetes, BDNF levels in the blood serum and nerve tissue are reduced, which correlates with the severity of the neuropathy [5].

Neurotrophin-3 (NT-3) is essential for the development and maintenance of proprioceptive neurons. A decrease in NT-3 levels in diabetes contributes to impaired deep sensation and motor coordination. Vascular endothelial growth factor (VEGF) supports nerve vascularization through the vasa nervorum. Impaired VEGF expression in diabetes exacerbates nerve tissue ischemia and slows the regeneration of damaged nerves [3, 21].

The pathophysiology of diabetic neuropathy involves a complex interplay of multiple metabolic, vascular, inflammatory, and trophic mechanisms. Chronic hyperglycemia, as the central pathogenetic factor, initiates a cascade of biochemical reactions leading to progressive damage of the peripheral nervous system. This review systematizes current understanding of the key

pathophysiological pathways in the development of diabetic neuropathy and their interrelationships.

Metabolic disturbances, including the activation of the polyol pathway, the formation of AGEs, and the activation of PKC, form the basis for the pathogenesis of diabetic neuropathy. Activation of the polyol pathway leads not only to osmotic stress from sorbitol accumulation but also to the depletion of antioxidant systems through reduced NADPH levels. The formation of AGEs triggers multiple pathological processes through interaction with RAGE, including the activation of pro-inflammatory signaling pathways, endothelial dysfunction, and impaired microcirculation. The activation of PKC modulates vascular tone and the expression of neurotrophic factors, thus linking metabolic disturbances with vascular pathology and impaired trophic support of the nerves.

Oxidative stress and mitochondrial dysfunction play a central role in nerve tissue damage. Excessive production of ROS damages cellular macromolecules, including DNA, proteins, and lipids, disrupting normal cell function. Mitochondrial dysfunction leads to an ATP deficit, which is especially critical for metabolically active neurons, and activates apoptotic pathways. A vicious cycle is formed when oxidative damage to mitochondria exacerbates ROS production, and the depletion of antioxidant systems makes cells even more vulnerable to oxidative stress.

Vascular mechanisms, including endothelial dysfunction and structural changes in the microvasculature, lead to ischemic nerve damage. Decreased NO bioavailability and increased endothelin-1 production impair vasodilation and reduce endoneurial blood flow. Thickening of the capillary basement membrane and disruption of the blood-nerve barrier limit the delivery of oxygen and nutrients to nerve fibers. Chronic hypoxia exacerbates the energy deficit, disrupts axonal transport, and contributes to nerve degeneration.

Inflammatory processes involving pro-inflammatory cytokines and the activation of immune cells make a significant contribution to the pathogenesis of diabetic neuropathy. Chronic subclinical inflammation, mediated by TNF- α , IL-1 β , and IL-6, has a direct damaging effect on neurons and sustains pathological processes in nerve tissue. The activation of macrophages and the production of chemokines recruit additional inflammatory cells, exacerbating the damage. This inflammatory response is closely linked to oxidative stress and endothelial dysfunction, forming mutually reinforcing pathological mechanisms.

Impaired neurotrophic support, manifesting as a deficiency in NGF and other growth factors, deprives neurons of the signals necessary for their survival and regeneration. Decreased expression and impaired axonal transport of neurotrophic factors lead to the progressive atrophy of axons and the loss of nerve fibers. Disrupted signaling of growth factors through receptor tyrosine kinases suppresses neuronal viability and regenerative capacity.

It is important to emphasize that the described pathophysiological mechanisms do not act in isolation but rather represent an integrated network of interconnected processes. Hyperglycemia activates all pathological pathways simultaneously, and these pathways interact, amplifying the damage to nerve tissue. For example, oxidative stress exacerbates the formation of AGEs, which in turn activate RAGE and induce additional ROS production. Endothelial dysfunction and microcirculatory disorders worsen hypoxia, which increases mitochondrial ROS production. Inflammatory cytokines suppress the expression of neurotrophic factors, and a deficit in trophic support makes neurons more vulnerable to oxidative and inflammatory damage.

Understanding the multifactorial nature of the pathogenesis of diabetic neuropathy has important clinical implications. It explains why glycemic control alone, although essential, is often insufficient to prevent or reverse neuropathy. This underscores the need for comprehensive therapeutic approaches that target multiple pathogenetic mechanisms. Modern treatment strategies include not only optimizing glycemia but also using antioxidants (α -lipoic acid), aldose reductase inhibitors, drugs that improve microcirculation, anti-inflammatory agents, and neurotrophic factors.

Promising areas of research include developing biomarkers for the early stages of neuropathy to allow for the timely initiation of pathogenetic therapy, and creating targeted drugs that selectively act on key pathophysiological mechanisms. Potential therapeutic targets include inhibitors of AGE formation and their receptors, modulators of the NF- κ B and PKC signaling pathways, mitochondria-targeted antioxidants, activators of neurotrophic signaling, and anti-inflammatory agents.

Diabetic neuropathy is a complex, multifactorial complication of diabetes mellitus that develops from the interaction of multiple pathophysiological mechanisms. Chronic hyperglycemia initiates a cascade of metabolic disturbances, including the activation of the polyol pathway, the formation of advanced glycation end products, and the activation of protein kinase C, which in turn trigger

oxidative stress, mitochondrial dysfunction, endothelial dysfunction, and chronic inflammation.

Oxidative stress and mitochondrial dysfunction play a central role in nerve tissue damage by causing energy deficiency, oxidative damage to macromolecules, and the activation of apoptotic pathways. Microvascular insufficiency, resulting from endothelial dysfunction and structural changes in the vasa nervorum capillaries, leads to chronic hypoxia and ischemic nerve damage. Inflammatory processes involving pro-inflammatory cytokines and immune cell activation exacerbate damage and perpetuate the chronic pathology. The disruption of neurotrophic support, manifested as a deficiency in nerve growth factors, deprives neurons of the signals necessary for survival and regeneration.

Thus, all the described mechanisms are closely interconnected and mutually reinforcing, forming an integrated network of pathological processes. This explains the progressive nature of diabetic neuropathy and justifies the need for comprehensive therapeutic approaches that target multiple pathogenetic mechanisms simultaneously.

A deep understanding of the pathophysiology of diabetic neuropathy creates new opportunities for early diagnosis, risk stratification, and the development of targeted therapies. Integrating knowledge of the molecular mechanisms of nerve damage with clinical data will enable the development of personalized approaches to preventing and treating this complication. Further research should focus on identifying biomarkers for the early stages of neuropathy, developing drugs with multi-targeted mechanisms of action, and conducting clinical trials of combined therapeutic strategies.

Only a comprehensive approach—encompassing optimal glycemic control, lifestyle modification, early diagnosis, and pathomechanism-based pharmacotherapy targeting multiple damage pathways—can ensure the effective prevention and slowing of diabetic neuropathy progression, thereby improving the quality of life and prognosis for patients with diabetes mellitus.

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