NEUROPATHY AND PREDIABETES

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https://doi.org/10.5281/zenodo.17462586

ARTICLE INFO

Received: 25th October 2025
Accepted: 26th October 2025
Online: 27th October 2025

KEYWORDS

prediabetes, type 2 diabetes, diabetes prevention, lifestyle modification

ABSTRACT

This article discusses diabetic neuropathy, one of the most common complications of diabetes mellitus (DM). According to several clinical studies, the prevalence of diabetic peripheral neuropathy is 30–50% among all patients with DM, and some authors believe that idiopathic neuropathy is a marker of prediabetes. The role of timely diagnosis and early initiation of therapy for the successful treatment of diabetic neuropathy and the prevention of serious complications of DM is emphasized.

Diabetic neuropathy (DN) is one of the most common chronic complications of diabetes mellitus (DM) and the most frequent form of neuropathy. According to several clinical studies, the prevalence of diabetic peripheral neuropathy (DPN) is 30-50% among all patients with DM.

For example, a multicenter study conducted at 118 clinics in the UK examined the prevalence of DN in a group of 6,487 patients with types 1 and 2 DM [1]. Among patients with type 1 DM, regardless of disease duration, the prevalence averaged 32%, while among patients with type 2 DM, it was 23%. The incidence of DN increased with increasing patient age and diabetes onset. Among patients with DM for less than 5 years, the prevalence was 21%, while among patients with DM for more than 10 years, the prevalence was 37%. While DN was diagnosed in only 5% of patients aged 20–29 years, its prevalence in the 70–79 age group was 44% [1]. However, the literature often contains conflicting data, the ambiguity of which is likely due to diverse and inadequate diagnostics with markedly varied clinical symptoms, the lack of standardized methods for identifying peripheral neuropathy, and studies of different patient groups.

Recently, we have often discussed the multifactorial management of type 2 diabetes, implying an impact on various stages of the disease's pathogenesis.

Pathogenesis of Diabetic Neuropathy

Currently, from a pathogenetic perspective, DN should be viewed more as a complex of multifactorial events, in the development of which glucose toxicity plays a central role (see figure).

Figure. Pathogenesis of Diabetic Neuropathy. The main pathogenetic mechanisms of DN development are:

Activation of the polyol pathway for glucose utilization leads to the accumulation of sorbitol and fructose, depletion of myoinositol, and decreased Na+/K+-ATPase activity. Since

glucose can enter nerve cells independently of insulin, it may not be fully involved in glycolysis, resulting in activation of the polyol pathway. Activation of the key enzyme aldose reductase results in increased amounts of sorbitol, which diffuses out of nerve cells or is oxidized by sorbitol dehydrogenase to form fructose.

It is the intracellular accumulation of sorbitol that causes various nerve damage. Thus, activation of the polyol pathway leads to depletion of the "second messenger" myoinositol.

Oxidative stress is one of the leading pathogenetic mechanisms in the development of DN, and it is currently receiving particular attention. Increased free radical formation, characteristic of diabetes, leads to disruption of the structure and function of nerve cells. Oxidative stress increases the amount of reactive oxygen species, or oxygen radicals, in a biological system. Normally, oxidative and antioxidant processes in the body are balanced, so free radicals constantly generated during oxidative stress are neutralized. Under hyperglycemic conditions, free radicals are formed during the "autoxidation" of glucose during the formation of advanced glycation end products. The rate of free radical formation depends on protein glycosylation status and, consequently, on the degree of hyperglycemia. The significance of free radicals lies in their increased capacity for chemical reactions. Free radicals react with unsaturated compounds, disrupting the structure of enzymatic proteins and lipids in cell membranes. In the early stages of oxidation, proteolysis and activation of lipid peroxidation predominate, leading to changes in the physicochemical properties of biological membranes. Subsequently, membrane lipid destruction develops, with hydrolytic enzymes penetrating from the damaged axon playing a major role. Excessive free radical formation, followed by damage to neuronal membrane structures and DNA, leads to impaired nerve cell function. Nerve tissue loses the ability to transport inositol, a compound necessary for the formation of myelin components. Endoneural hypoxia, caused by microcirculation pathology, increases free radical activity, which in turn leads to thrombogenic transformation of the vascular endothelium (through activation of the transcription factor NF-kB) and alters the structure of capillary walls, exacerbating endoneural hypoxia.

The toxicity of free radicals is limited in the presence of "radical traps," and peroxide levels are maintained at a low level by their participation in metabolic reactions as intermediaries or by converting them into stable molecules. Increased free radical processes are one of the three Trigger mechanisms leading to nitric oxide (NO) deficiency in diabetes. It is believed that the earliest impairments of endothelial function and vasodilation are primarily associated with impaired synthesis, release, and/or effects of endothelial NO. Free radicals can directly destroy NO. Furthermore, increased membrane lipid peroxidation leads to damage to the endothelium's structure and impairment of its NO-producing capacity. An absolute or relative deficiency of NO, which is necessary for the normal regulation of vascular tone, develops. A weakening of NO-dependent vasodilatory responses leads to increased vascular tone, vasoconstriction, and a subsequent decrease in oxygen pressure in peripheral nerves in patients with diabetes.

Disturbances in the metabolism of n-6 essential fatty acids and prostaglandins, leading to changes in the structure of neuronal membranes, impaired capillary function, and impaired blood rheology. Impaired fatty acid metabolism leads to disturbances in the cyclooxygenase

cycle, reduced production of vasoactive substances, and thus to impaired endoneural blood flow.

The permeability of the blood/nerve barrier to glycosylated albumin, which forms in patients with DN, may be increased (Poduslo, 1992). Glycosylated macromolecules, elevated concentrations of which are observed in the endoneurium, can lead to neuropathy through direct toxicity, osmotic changes, or immunological mechanisms.

Non-enzymatic protein glycosylation is based on the ability of glucose, fructose, and galactose to undergo glycosylation reactions with amino groups found in proteins, lipids, and nucleic acids. As a result, reversible Schiff bases are formed between sugar molecules and the amino groups of proteins, lipids, and DNA through the Maillard reaction. These products form Amadori products, which create advanced glycosylation end products (AGEs) (Bierhaus, 2004), after undergoing a complex series of chemical transformations. These products, through intra- and intermolecular bonds, cause irreversible structural changes, including those of proteins, and lead to functional impairment. Here, the protein glycosylation theory intertwines with the free radical theory: the formation of AGEs in the cell increases the level of free radicals by 50-fold.

Weakening of neurotrophism, leading to decreased expression and depletion of neurotrophic factors such as nerve growth factor, neurotrophin-3, and insulin-like growth factor, and impaired axonal transport.

Immune reactions with the formation of autoantibodies to the vagus nerve, sympathetic ganglia, and adrenal medulla (Rabinowe, 1990), as well as inflammatory processes.

C-peptide. A decrease in the insulin/C-peptide ratio is considered a possible pathogenetic pathway in the development of DPN. Preclinical studies have demonstrated the broad physiological effects of C-peptide, namely, its influence on the activity of Na+/K+-ATPase, endothelial NO synthase, the expression of neurotrophic factors, the regulation of molecular mechanisms underlying nerve degeneration in patients with type 1 diabetes, the interaction of transcription factors with DNA, and an effect on apoptosis. A study of patients with type 1 diabetes who received subcutaneous injections of C-peptide for 12 weeks revealed a significant improvement in impulse conduction velocity along sensory fibers of the sural nerve and an improvement in vibration sensitivity without changes in temperature sensitivity. The effectiveness of C-peptide in the treatment of DPN in type 2 diabetes is questionable and unproven, requiring further research in this area [2-6].

Diabetic foot syndrome (DN) is a progressive disease that, without adequate treatment, leads to the development of diabetic foot syndrome (DF). DN is therefore a comorbid condition associated with diabetes, causing increased morbidity and mortality. The healthcare system spends approximately €1 billion on treating patients with DN. The high cost of DN treatment is primarily due to delayed diagnosis, as DN is typically detected at the stage of irreversible changes and clinically evident symptoms. DN treatment may need to be initiated well before the onset of its first symptoms.

There is a traditional view that DN develops after many years of persistent hyperglycemia. However, according to some literature data, DN is diagnosed in 20% or more of patients with newly diagnosed diabetes based on electrophysiological studies, while

diabetic retinopathy and nephropathy are virtually absent. Idiopathic neuropathy, according to a number of authors, is a marker of prediabetes [6]. Experiments on laboratory animals and humans have shown that transient hyperglycemia increases spontaneous discharge from small diameter nociceptive afferent C-fibers and is clinically associated with increased neuropathic pain [7, 8].

Interesting data were obtained in a 2009 study by Dan Ziegler et al. conducted at the Leibniz Institute of Clinical Diabetology. The aim of the study was to determine the prevalence and risk factors for the development of neuropathic pain in patients with diabetes, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or normal glucose tolerance. The study involved 393 volunteers with symptoms of neuropathy. The study population was divided into 2 groups: patients with diabetes (n = 195) and a control group (n = 198). Both groups were matched for age and gender. In the control group, 44 (23.9%) patients had a combination of IFG and IGT; Of these, 71 (35.9%) patients were diagnosed with IFG and 81 with IGT. The prevalence (95% confidence interval) of neuropathic pain was 13.4% (8.9-18.3) for patients with diabetes, 8.7% (2.4-20) for individuals with IFG, and 1.2% (0.03-6.7) for patients with IFG (p = 0.0003). In the entire population (n = 393), age, body weight, peripheral arterial disease, and diabetes were considered risk factors significantly associated with neuropathic pain, in contrast to the group with diabetes, where only age, body weight, and peripheral arterial disease were associated with this. Thus, the prevalence of neuropathic pain increased by 2-3 times in patients with IFG and diabetes compared to the IFG group. With the exception of diabetes, the predominant risk factors include age, obesity, and peripheral arterial disease.

Furthermore, the study demonstrated for the first time that DN is an independent factor associated with waist circumference and peripheral arterial disease. For example, a 1-cm increase in waist circumference was shown to be associated with a 4% increase in the likelihood of developing neuropathy [9]. However, these results do not confirm the data of other studies [10].

According to some authors, 25–62% of patients with idiopathic neuropathy have prediabetes; of these, peripheral neuropathy develops in 11–25%, and neuropathic pain in 13–21%. The most sensitive test for assessing glucose metabolism is the oral glucose tolerance test (OGTT). Individuals with prediabetes have less severe complications than patients with established diabetes. The main pathogenetic mechanisms for the development of neuropathy are hyperglycemia, microvascular complications, dyslipidemia, and metabolic syndrome. Sensory impairments in diabetic neuropathy are detected earlier than motor impairments and are relatively easy to detect. The diagnosis of diabetic neuropathy should be based on a thorough clinical and electrophysiological examination. OGTT should be performed in all patients with idiopathic neuropathy [11].

Neurometabolic therapy for the neurological complications of diabetes is of great interest to both clinicians and physiologists. Recently, new clinical and experimental data have emerged that support the use of this group of drugs in patients with diabetic polyneuropathy.The known mechanisms of action of Actovegin have generated interest in its use in patients with diabetes, as cellular pathology in this disease is associated with both metabolic disturbances and altered blood flow in the microcirculation system [12, 13]. The

main studies evaluating the efficacy of Actovegin were conducted in diabetic peripheral nerve damage—diabetic distal symmetric sensorimotor polyneuropathy (DPN) [14–16].

W. Jansen and E. Beck studied the effects of oral Actovegin in patients with diabetes mellitus and DPN in a controlled study: one group of 35 patients received placebo, while the other group of 35 patients received Actovegin tablets (600 mg 3 times daily) for 24 weeks [16]. The criteria for evaluating the drug's efficacy included clinical characteristics of polyneuropathy (tendon reflexes, superficial and deep sensitivity, pain intensity) and electromyographic indices of peripheral nerve function (velocity of nerve conduction, as well as the distance the patients could walk without pain). Improvement in the condition of patients in the Actovegin treatment group was noted in the majority of patients 8 weeks after the start of treatment, with the optimal effect achieved after 16 weeks of treatment. Significant improvements were demonstrated with Actovegin treatment compared to the placebo group in virtually all clinical parameters: pain-free walking distance, tendon reflexes, and superficial and deep sensitivity ($p < 0.01$). The rate of arousal propagation significantly ($p < 0.001$) increased in the treatment group compared to the placebo group. Patients in the treatment group felt better and reported fewer complaints of psychoemotional disturbances, which correlated with an improvement in their physical condition.

In 2009, the results of a randomized, double-blind, placebo-controlled trial were published.A study of the treatment of patients with type 2 diabetes and DPN with Actovegin was conducted at 26 clinical centers in Russia, Ukraine, and Kazakhstan. The clinical efficacy and safety of Actovegin were assessed in patients with type 2 diabetes and clinical manifestations of DPN. A total of 567 patients were included in the study: 281 patients initially received 20 intravenous infusions of Actovegin (250 ml of a 20% solution), and then received Actovegin pills 600 mg three times daily for 140 days. 286 patients with diabetes and DPN received intravenous placebo therapy, followed by pill therapy with placebo. The primary efficacy endpoints in this study included patient complaints of numbness, pain, burning, and pins and needles, assessed using a neuropathic impairment scale, and the vibration threshold, which was measured at several points on the legs using a biotensiometer. Secondary efficacy endpoints included a neurological symptom scale and quality of life measures. The best results were observed for leg discomfort, with improvements noted both in the overall symptom score and for each individual symptom. A significant reduction in sensory neurological deficits was observed. The reduction in vibration threshold was highly significant with Actovegin compared to placebo. Fasting glucose and glycated hemoglobin levels were measured throughout the study. These results suggest that Actovegin's efficacy is related to the drug's action and not to changes in diabetes control. No significant adverse events were observed in the study. A significant improvement in quality of life (as measured by a mental health scale) was demonstrated in the Actovegin group compared to placebo. It was noted that the Actovegin and placebo groups had comparable safety profiles. The U.S. Food and Drug Administration (FDA) has developed specific criteria for drugs that can be registered for the treatment of DPN:

- action on pathogenic mechanisms,
- reduction of neuropathy symptoms,
- improvement of nerve function,

- absence of significant side effects,
- reduction of the risk of nerve fiber death.

The studies conducted suggest that Actovegin meets most of these criteria and can be used for the treatment of DPN [17, 18].

In summary, only timely diagnosis and early initiation of therapy can successfully achieve the goal of treating DPN. In addition, there is a need for further research to more accurately determine the epidemiological link between NTG and idiopathic neuropathy in order to develop specific measures aimed at preventing the development of more serious complications of diabetes - lower limb amputations.

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