

Pathogenetic Mechanisms and Clinical Manifestations of Diabetic Peripheral Polyneuropathy in Type 2 Diabetes Mellitus

Xaydarova Xilolaxon Ravshan qizi, Xolmatova Gulxayo Azimjonovna-

Associate Professor, PhD in Medical Sciences, Department of Hospital Therapy and Endocrinology,
Andijan State Medical Institute, Andijan, Uzbekistan

Abstract

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder that has become one of the leading global health challenges due to its rapidly increasing prevalence and numerous long-term complications. Among these complications, diabetic peripheral polyneuropathy (DPN) is the most common neurological disorder, affecting approximately one-third to one-half of patients with diabetes. DPN is characterized by progressive degeneration of peripheral nerves resulting from complex metabolic, vascular, inflammatory, and neurodegenerative processes initiated by persistent hyperglycemia.

The pathogenesis of diabetic peripheral polyneuropathy involves multiple interconnected mechanisms, including activation of the polyol pathway, excessive formation of advanced glycation end products, oxidative stress, mitochondrial dysfunction, chronic inflammation, endothelial impairment, and microvascular ischemia. These pathological changes ultimately lead to axonal degeneration, segmental demyelination, impaired nerve conduction, and irreversible neuronal damage.

Clinically, diabetic peripheral polyneuropathy presents with distal symmetric sensory loss, paresthesia, burning pain, numbness, muscle weakness, impaired proprioception, and reduced tendon reflexes. Disease progression significantly increases the risk of diabetic foot syndrome, recurrent ulceration, infection, lower-limb amputation, and reduced quality of life.

Early diagnosis using neurological examination, quantitative sensory testing, nerve conduction studies, and validated clinical scoring systems remains crucial for preventing irreversible complications. Current treatment strategies combine strict glycemic control with pathogenetic therapies, antioxidant agents, symptomatic pain management, lifestyle modification, and comprehensive foot care. Emerging therapeutic approaches targeting oxidative stress, neuroinflammation, mitochondrial dysfunction, and nerve regeneration offer promising opportunities for improving long-term outcomes.

This review summarizes current knowledge regarding the epidemiology, pathogenetic mechanisms, clinical manifestations, diagnostic approaches, and modern therapeutic strategies for diabetic peripheral polyneuropathy associated with type 2 diabetes mellitus.

Keywords: Type 2 diabetes mellitus; diabetic peripheral neuropathy; pathogenesis; oxidative stress; inflammation; microvascular dysfunction; neuropathic pain; treatment.

1. Introduction

Type 2 diabetes mellitus (T2DM) represents one of the fastest-growing chronic diseases worldwide and poses a significant burden on healthcare systems because of its increasing prevalence, high morbidity, and substantial economic costs. According to recent estimates from the International Diabetes Federation, more than 530 million adults currently live with diabetes, and this number is projected to exceed 780 million by 2045. Approximately 90–95% of all diabetes cases are classified as type 2 diabetes mellitus, which is closely associated with obesity, sedentary lifestyle, population aging, and genetic susceptibility[1,5].

Persistent hyperglycemia leads to progressive damage of multiple organ systems, including the cardiovascular, renal, ophthalmologic, and nervous systems. Among the chronic neurological complications, diabetic peripheral polyneuropathy (DPN) is the most prevalent, affecting nearly 50% of patients with long-standing diabetes. The prevalence of DPN increases with disease duration, poor glycemic control, hypertension, dyslipidemia, smoking, obesity, and advanced age.

Diabetic peripheral polyneuropathy is defined as a symmetrical, length-dependent sensorimotor polyneuropathy caused by chronic metabolic disturbances associated with diabetes. The disorder develops gradually and primarily affects the longest peripheral nerve fibers, resulting in characteristic "stocking-and-

glove" sensory impairment. Although initially asymptomatic in many patients, progressive nerve injury eventually causes numbness, burning sensations, tingling, electric shock-like pain, muscle weakness, impaired balance, and gait disturbances[4,8].

The pathophysiology of diabetic peripheral polyneuropathy is considerably more complex than previously recognized. Chronic hyperglycemia initiates several biochemical pathways that contribute to neuronal injury. Increased intracellular glucose activates the polyol pathway, leading to sorbitol accumulation, osmotic stress, and depletion of intracellular antioxidants. Simultaneously, excessive production of advanced glycation end products alters protein structure and receptor signaling, promoting oxidative damage and inflammation. Mitochondrial dysfunction further amplifies reactive oxygen species generation, resulting in lipid peroxidation, DNA damage, and apoptosis of neuronal cells. Endothelial dysfunction and impaired microvascular circulation reduce oxygen delivery to peripheral nerves, accelerating axonal degeneration.

Inflammatory mechanisms also play an essential role in disease progression. Elevated circulating levels of tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), interleukin-1 β (IL-1 β), and nuclear factor-kappa B contribute to chronic neuroinflammation and degeneration of peripheral nerve fibers. Recent studies additionally suggest that dyslipidemia, insulin resistance, impaired lipid metabolism, and alterations in the gut microbiome may further exacerbate neuronal dysfunction independently of hyperglycemia[2,9].

Clinically, diabetic peripheral polyneuropathy substantially reduces patients' quality of life. Neuropathic pain often interferes with sleep, physical activity, emotional well-being, and occupational performance. Loss of protective sensation markedly increases the risk of foot ulceration, infection, Charcot neuroarthropathy, and lower-extremity amputation, making diabetic neuropathy one of the leading causes of disability among individuals with diabetes.

Despite significant advances in diabetes management, diabetic peripheral polyneuropathy remains underdiagnosed, particularly during its early stages when therapeutic interventions are most effective. Consequently, increasing attention has been directed toward identifying novel biomarkers, improving diagnostic accuracy, and developing pathogenetically targeted therapies capable of slowing or reversing nerve damage.

This review aims to summarize current evidence regarding the epidemiology, molecular pathogenesis, clinical manifestations, diagnostic methods, and modern treatment strategies for diabetic peripheral polyneuropathy in patients with type 2 diabetes mellitus while highlighting emerging therapeutic perspectives that may improve clinical outcomes in the future[10].

2. Epidemiology and Risk Factors

Diabetic peripheral polyneuropathy (DPN) is the most common chronic neurological complication of type 2 diabetes mellitus (T2DM) and one of the leading causes of disability among diabetic patients. The prevalence of DPN has increased steadily over the past decades, reflecting the global rise in diabetes incidence, population aging, sedentary lifestyles, and obesity. According to the International Diabetes Federation (IDF), more than 537 million adults worldwide were living with diabetes in 2021, and this number is expected to exceed 783 million by 2045. Approximately 90–95% of these cases represent T2DM, making diabetic neuropathy an increasingly important public health concern.

The reported prevalence of diabetic peripheral polyneuropathy varies considerably depending on diagnostic criteria, patient characteristics, disease duration, and methods of neurological assessment. Large epidemiological studies indicate that DPN affects approximately 20–30% of patients at the time of diagnosis of T2DM and more than 50% of individuals with disease duration exceeding ten years. In some populations, the prevalence reaches 60–70% among elderly patients with poorly controlled diabetes. Importantly, up to half of affected individuals remain asymptomatic during the early stages, delaying diagnosis and increasing the risk of irreversible nerve damage.

The development of diabetic peripheral polyneuropathy is influenced by numerous metabolic, vascular, genetic, and lifestyle-related factors. Chronic hyperglycemia remains the principal risk factor because prolonged exposure to elevated blood glucose initiates multiple biochemical pathways responsible for neuronal injury. Numerous clinical studies have demonstrated a strong positive correlation between glycated hemoglobin (HbA1c) levels and both the incidence and severity of neuropathy. Each 1% increase in HbA1c significantly elevates the risk of peripheral nerve dysfunction[6].

Duration of diabetes is another well-established determinant of neuropathy. Patients with diabetes for more than ten years exhibit a substantially higher prevalence of sensory and motor nerve impairment than those with recently diagnosed disease. Persistent metabolic imbalance over time results in cumulative oxidative stress, progressive microvascular dysfunction, and irreversible axonal degeneration.

Age also plays an independent role in disease development. Elderly patients experience accelerated neuronal degeneration due to physiological aging of peripheral nerves combined with diabetes-induced metabolic disturbances. Furthermore, obesity and insulin resistance contribute to chronic low-grade inflammation and lipid metabolism abnormalities that aggravate peripheral nerve injury even before overt hyperglycemia develops.

Cardiovascular risk factors, including hypertension, dyslipidemia, smoking, and physical inactivity, significantly increase the likelihood of diabetic neuropathy. Elevated triglycerides and low-density lipoprotein cholesterol promote endothelial dysfunction and microvascular ischemia, reducing oxygen and nutrient delivery to peripheral nerves. Cigarette smoking further impairs vascular function by increasing oxidative stress and inflammatory cytokine production[7].

Recent investigations have highlighted the contribution of chronic kidney disease, metabolic syndrome, vitamin B12 deficiency, non-alcoholic fatty liver disease, and obstructive sleep apnea to the progression of diabetic neuropathy. Genetic susceptibility has also been proposed, with polymorphisms affecting antioxidant defense systems, inflammatory mediators, mitochondrial enzymes, and neurotrophic factors potentially influencing individual vulnerability to nerve injury.

From a clinical perspective, diabetic peripheral polyneuropathy is associated with considerable morbidity and healthcare expenditure. Neuropathic pain reduces physical activity, impairs sleep quality, increases anxiety and depression, and markedly diminishes health-related quality of life. Loss of protective sensation predisposes patients to diabetic foot ulcers, infections, Charcot neuroarthropathy, and lower-extremity amputations, making DPN one of the most costly complications of diabetes worldwide[5].

Because many modifiable risk factors contribute to disease progression, early screening, optimal glycemic control, cardiovascular risk reduction, lifestyle modification, and patient education remain fundamental strategies for preventing or delaying diabetic peripheral neuropathy.

3. Pathogenetic Mechanisms

Diabetic peripheral polyneuropathy is a multifactorial disorder resulting from the interaction of metabolic abnormalities, vascular dysfunction, oxidative stress, neuroinflammation, and impaired nerve regeneration. Chronic hyperglycemia initiates several interconnected biochemical pathways that collectively damage peripheral neurons, Schwann cells, endothelial cells, and supporting connective tissues. Rather than a single pathogenic mechanism, diabetic neuropathy develops through the cumulative effects of multiple molecular disturbances that progressively impair neuronal structure and function.

3.1 Chronic Hyperglycemia

Persistent hyperglycemia represents the primary initiating factor in diabetic neuropathy. Excess intracellular glucose overwhelms normal metabolic pathways and activates several alternative biochemical processes that produce toxic metabolites. Continuous glucose overload disrupts neuronal energy metabolism, increases reactive oxygen species (ROS) production, and accelerates cellular apoptosis. Hyperglycemia also impairs axonal transport and reduces the synthesis of neurotrophic factors essential for neuronal survival.

3.2 Activation of the Polyol Pathway

Under hyperglycemic conditions, excess glucose is converted into sorbitol by the enzyme aldose reductase. Sorbitol is subsequently metabolized into fructose by sorbitol dehydrogenase. Intracellular accumulation of sorbitol causes osmotic stress, cellular edema, depletion of myo-inositol, and reduced Na^+/K^+ -ATPase activity. These alterations impair nerve conduction velocity and disrupt normal neuronal signaling. Additionally, increased consumption of NADPH during sorbitol synthesis reduces glutathione regeneration, weakening antioxidant defense mechanisms[6].

3.3 Advanced Glycation End Products (AGEs)

Long-term hyperglycemia promotes non-enzymatic glycation of proteins, lipids, and nucleic acids, resulting in the formation of advanced glycation end products (AGEs). These molecules accumulate within peripheral nerves and vascular tissues, altering extracellular matrix composition and reducing tissue elasticity. Binding

of AGEs to their receptor (RAGE) activates intracellular signaling pathways involving nuclear factor-kappa B (NF- κ B), which stimulates the production of pro-inflammatory cytokines, adhesion molecules, and reactive oxygen species. Consequently, chronic inflammation and vascular injury accelerate neuronal degeneration.

3.4 Oxidative Stress

Oxidative stress is widely recognized as the central mechanism responsible for diabetic nerve injury. Hyperglycemia increases mitochondrial production of superoxide radicals while simultaneously reducing antioxidant enzyme activity. Excessive reactive oxygen species damage membrane lipids, proteins, and mitochondrial DNA, leading to impaired cellular respiration and apoptosis. Lipid peroxidation further disrupts neuronal membrane integrity and contributes to axonal degeneration. Reduced levels of glutathione, superoxide dismutase, and catalase aggravate oxidative damage, making antioxidant therapy an important pathogenetic approach.

3.5 Mitochondrial Dysfunction

Mitochondria play a crucial role in maintaining neuronal energy metabolism. Chronic oxidative stress damages mitochondrial DNA, decreases ATP synthesis, and disrupts calcium homeostasis. Dysfunctional mitochondria generate even greater quantities of reactive oxygen species, creating a vicious cycle of oxidative injury. Energy deficiency particularly affects long peripheral axons because of their high metabolic demands, explaining the characteristic distal distribution of diabetic neuropathy[5].

3.6 Protein Kinase C Activation

Elevated intracellular glucose increases diacylglycerol synthesis, leading to activation of protein kinase C (PKC). Activated PKC alters vascular permeability, reduces nitric oxide production, increases vasoconstriction, and stimulates extracellular matrix deposition. These vascular abnormalities impair endoneurial blood flow and contribute to chronic ischemia of peripheral nerves.

3.7 Chronic Inflammation

Increasing evidence indicates that diabetic neuropathy is partly an inflammatory disease. Hyperglycemia stimulates macrophages, Schwann cells, and endothelial cells to release pro-inflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6). Persistent activation of inflammatory pathways promotes neuronal apoptosis, demyelination, and impaired axonal regeneration. Elevated inflammatory biomarkers have been correlated with increased neuropathy severity and neuropathic pain intensity.

3.8 Endothelial Dysfunction and Microvascular Ischemia

Peripheral nerves depend on an extensive microvascular network for adequate oxygen and nutrient supply. Diabetes-induced endothelial dysfunction reduces nitric oxide bioavailability while increasing endothelin-1 production, resulting in vasoconstriction and impaired blood flow. Thickening of capillary basement membranes and decreased capillary density further compromise endoneurial perfusion. Chronic ischemia contributes to axonal degeneration, demyelination, and reduced nerve conduction velocity[8].

3.9 Impaired Neuroregeneration

Under physiological conditions, peripheral nerves possess a considerable capacity for regeneration following injury. However, diabetes significantly reduces this regenerative potential by decreasing the expression of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), and other neurotrophic molecules. Impaired Schwann cell function further limits remyelination and axonal repair, allowing progressive neurological deterioration.

Overall, diabetic peripheral polyneuropathy develops through the interaction of metabolic, vascular, oxidative, inflammatory, and neurodegenerative mechanisms. Understanding these complex pathogenetic pathways provides the foundation for developing targeted therapeutic strategies aimed not only at relieving symptoms but also at slowing disease progression and promoting nerve regeneration[8].

4. Clinical Manifestations

Diabetic peripheral polyneuropathy (DPN) is a chronic, progressive, length-dependent sensorimotor neuropathy that primarily affects the distal portions of the lower extremities before involving the upper limbs. The disease usually develops gradually and may remain asymptomatic for several years, making early diagnosis challenging. Clinical manifestations vary depending on the severity of nerve injury and the involvement of sensory, motor, and autonomic nerve fibers.

Sensory symptoms are the earliest and most common manifestations of DPN. Patients frequently complain of numbness, tingling, burning sensations, electric shock-like pain, stabbing discomfort, and hypersensitivity to touch. These symptoms usually begin in the toes and feet and gradually progress proximally in a characteristic "stocking" distribution. As the disease advances, similar symptoms may appear in the hands, resulting in the classic "stocking-and-glove" pattern. Neuropathic pain often worsens during the night, causing sleep disturbances, fatigue, anxiety, and depression.

Progressive sensory fiber degeneration leads to impaired vibration perception, reduced proprioception, diminished temperature discrimination, and loss of protective sensation. Consequently, patients become unable to detect minor trauma, pressure, or thermal injury, substantially increasing the risk of foot ulceration and infection. Physical examination commonly demonstrates reduced ankle reflexes, impaired vibration sense assessed with a 128-Hz tuning fork, decreased pinprick sensation, and abnormal monofilament testing[5].

Motor involvement usually develops during later stages of the disease. Weakness of intrinsic foot muscles contributes to muscle wasting, toe deformities, altered gait, and impaired balance. Progressive motor dysfunction may eventually result in foot instability and increased susceptibility to falls.

Autonomic neuropathy frequently accompanies peripheral nerve damage in patients with long-standing diabetes. Clinical manifestations include orthostatic hypotension, resting tachycardia, gastrointestinal dysmotility, constipation, diarrhea, urinary bladder dysfunction, erectile dysfunction, impaired sweating, and reduced cardiovascular autonomic regulation. Autonomic dysfunction significantly increases morbidity and mortality, particularly because of its association with silent myocardial ischemia and sudden cardiac death.

The severity of clinical manifestations generally correlates with disease duration, glycemic control, cardiovascular risk factors, and the degree of oxidative stress. Nevertheless, symptom severity does not always correspond to the extent of nerve damage, emphasizing the importance of objective neurological assessment. Early recognition of neuropathic symptoms remains essential because timely intervention may delay disease progression and prevent disabling complications such as diabetic foot syndrome and lower-extremity amputation[8].

5. Diagnosis

Early diagnosis of diabetic peripheral polyneuropathy is crucial because structural nerve damage often precedes the onset of clinical symptoms. Current international guidelines recommend annual screening for neuropathy in all patients with type 2 diabetes beginning at the time of diagnosis. Comprehensive evaluation includes detailed medical history, neurological examination, laboratory assessment, and specialized neurophysiological investigations.

Clinical diagnosis begins with careful evaluation of neuropathic symptoms, including pain characteristics, sensory disturbances, muscle weakness, balance impairment, and autonomic complaints. Standardized questionnaires such as the Michigan Neuropathy Screening Instrument (MNSI), Neuropathy Symptom Score (NSS), Neuropathy Disability Score (NDS), Toronto Clinical Neuropathy Score (TCNS), and Douleur Neuropathique 4 (DN4) questionnaire facilitate early detection and grading of disease severity[4].

Neurological examination includes assessment of vibration sensation using a 128-Hz tuning fork, pressure perception with a 10-g Semmes-Weinstein monofilament, pinprick sensation, temperature discrimination, proprioception, and deep tendon reflexes, particularly the Achilles reflex. Loss of protective sensation identified by monofilament testing is considered one of the strongest predictors of diabetic foot ulceration.

Nerve conduction studies (NCS) remain the gold standard for confirming large-fiber neuropathy. These studies evaluate sensory and motor nerve conduction velocity, distal latency, and action potential amplitude, providing objective evidence of axonal degeneration and demyelination. Electromyography (EMG) may further characterize neuromuscular involvement.

Assessment of small-fiber neuropathy requires more specialized techniques because conventional nerve conduction studies may remain normal during early disease stages. Quantitative sensory testing (QST), skin biopsy for intraepidermal nerve fiber density, corneal confocal microscopy, and laser-evoked potentials are increasingly utilized for detecting early small-fiber dysfunction.

Laboratory investigations focus on identifying contributing metabolic abnormalities and excluding alternative causes of neuropathy. Routine evaluation includes fasting plasma glucose, glycated hemoglobin (HbA1c),

lipid profile, renal and hepatic function tests, thyroid function, vitamin B12 concentration, folate levels, and inflammatory markers when clinically indicated[3].

A multidisciplinary diagnostic approach combining clinical assessment, neurophysiological testing, and laboratory evaluation provides the highest diagnostic accuracy and allows early implementation of appropriate therapeutic interventions.

6. Modern Treatment Strategies

Management of diabetic peripheral polyneuropathy requires a comprehensive approach aimed at slowing disease progression, relieving neuropathic pain, improving nerve function, preventing foot complications, and enhancing patients' quality of life. Because nerve damage results from multiple pathogenic mechanisms, treatment should combine metabolic control with pathogenetically targeted and symptomatic therapies.

Optimal glycemic control remains the cornerstone of DPN management. Numerous clinical trials have demonstrated that maintaining glycated hemoglobin levels close to recommended targets significantly reduces the incidence and progression of diabetic neuropathy. Intensive glucose control decreases activation of pathogenic metabolic pathways, reduces oxidative stress, and improves microvascular function. Modern glucose-lowering agents, including sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have demonstrated additional cardiovascular and renal benefits, although their direct neuroprotective effects remain under investigation.

Pathogenetic therapy aims to interrupt the molecular mechanisms responsible for nerve injury. Alpha-lipoic acid is one of the most extensively studied antioxidant agents in diabetic neuropathy. It neutralizes reactive oxygen species, improves mitochondrial function, enhances endoneurial blood flow, and increases nerve conduction velocity. Clinical trials have shown that intravenous administration followed by oral maintenance therapy significantly reduces neuropathic pain and sensory impairment[4].

Benfotiamine, a lipid-soluble derivative of vitamin B1, inhibits several hyperglycemia-induced metabolic pathways, including advanced glycation end-product formation and protein kinase C activation. Supplementation with B-group vitamins, particularly methylcobalamin (vitamin B12), pyridoxine (vitamin B6), and thiamine (vitamin B1), supports neuronal metabolism, myelin repair, and axonal regeneration, especially in patients with documented vitamin deficiencies.

Symptomatic treatment of neuropathic pain is recommended when pain significantly interferes with daily functioning. Current international guidelines recommend duloxetine, pregabalin, and gabapentin as first-line pharmacological therapies. Duloxetine enhances descending inhibitory pain pathways by increasing serotonin and norepinephrine availability, whereas pregabalin and gabapentin reduce neuronal excitability through modulation of voltage-gated calcium channels. Tricyclic antidepressants may also be effective in selected patients but are often limited by adverse cardiovascular and anticholinergic effects[7].

Topical therapies, including high-concentration capsaicin patches and lidocaine patches, may provide localized pain relief with minimal systemic adverse effects. Opioid analgesics are generally discouraged because of limited long-term efficacy and substantial risks of dependence and adverse events.

Lifestyle modification represents another essential component of treatment. Regular aerobic exercise, resistance training, weight reduction, smoking cessation, and dietary optimization improve insulin sensitivity, vascular function, and inflammatory status while enhancing overall neurological health. Structured exercise programs have demonstrated improvements in nerve conduction, balance, muscle strength, and quality of life[9].

Comprehensive diabetic foot care is fundamental for preventing ulceration and amputation. Patients should receive education regarding daily foot inspection, proper footwear, skin care, and prompt reporting of minor injuries. Regular podiatric evaluation significantly reduces the incidence of diabetic foot complications.

Emerging therapeutic approaches include stem cell therapy, mesenchymal stromal cell transplantation, gene therapy, exosome-based treatment, neurotrophic growth factors, mitochondrial-targeted antioxidants, anti-inflammatory biological agents, and regenerative medicine strategies. Although many of these interventions remain experimental, they represent promising directions for future disease-modifying therapies.

7. Future Perspectives

Future research should focus on identifying reliable biomarkers for early diagnosis and monitoring disease progression. Advances in molecular biology, genomics, proteomics, metabolomics, and artificial intelligence are expected to improve individualized risk assessment and facilitate precision medicine approaches.

Novel therapeutic strategies targeting oxidative stress, chronic inflammation, mitochondrial dysfunction, and impaired neuroregeneration may provide opportunities not only to alleviate symptoms but also to reverse nerve damage. Personalized treatment algorithms integrating metabolic, genetic, and clinical characteristics may further optimize long-term outcomes in patients with diabetic peripheral polyneuropathy[10].

8. Conclusion

Diabetic peripheral polyneuropathy remains one of the most prevalent and disabling chronic complications of type 2 diabetes mellitus. The disorder develops through a complex interaction of persistent hyperglycemia, oxidative stress, advanced glycation, mitochondrial dysfunction, endothelial injury, inflammation, and impaired neuroregeneration. These mechanisms progressively damage peripheral nerve fibers, leading to sensory loss, neuropathic pain, motor dysfunction, autonomic impairment, and an increased risk of diabetic foot syndrome.

Early recognition of clinical manifestations through comprehensive neurological assessment and appropriate neurophysiological investigations is essential for preventing irreversible nerve injury. Current management strategies emphasize strict glycemic control, pathogenetic therapy, symptomatic pain management, lifestyle modification, and multidisciplinary foot care. While existing treatments primarily slow disease progression and relieve symptoms, ongoing advances in regenerative medicine, molecular therapeutics, and precision medicine offer promising prospects for disease-modifying interventions.

A deeper understanding of the molecular pathogenesis of diabetic peripheral polyneuropathy will facilitate the development of more effective diagnostic tools and targeted therapies, ultimately improving neurological outcomes, reducing disability, and enhancing the quality of life of patients with type 2 diabetes mellitus.

References

1. Sloan G, Selvarajah D, Tesfaye S. Pathogenesis, diagnosis and clinical management of diabetic sensorimotor peripheral neuropathy. *Nature Reviews Endocrinology*. 2021;17(7):400–420.
2. Yang Y, Zhao B, Wang Y, Lan H, Liu X, Hu Y, et al. Diabetic neuropathy: cutting-edge research and future directions. *Signal Transduction and Targeted Therapy*. 2025;10:132.
3. Savelieff MG, Elafros MA, Viswanathan V, Jensen TS, Bennett DL, Feldman EL, et al. The global and regional burden of diabetic peripheral neuropathy. *Nature Reviews Neurology*. 2025;21(1):17–31.
4. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW, Wright DE, Bennett DL, et al. Diabetic neuropathy. *Nature Reviews Disease Primers*. 2019;5:41.
5. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. *Diabetes Care*. 2017;40(1):136–154.
6. American Diabetes Association Professional Practice Committee. Standards of Care in Diabetes—2025. *Diabetes Care*. 2025;48(Suppl. 1):S1–S350.
7. International Diabetes Federation. IDF Diabetes Atlas. 11th ed. Brussels, Belgium: International Diabetes Federation; 2025.
8. Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. *Diabetes Care*. 2010;33(10):2285–2293.
9. Calcutt NA. Diabetic neuropathy and neuropathic pain: a (con)fusion of pathogenic mechanisms? *Pain*. 2020;161(Suppl 1):S65–S86.
10. Ziegler D. Pathogenetic treatments for diabetic peripheral neuropathy. *Diabetes Research and Clinical Practice*. 2023;206:110764.