

MODERN APPROACHES TO THE TREATMENT OF DIABETIC POLYNEUROPATHY: INTEGRATED NEUROLOGICAL AND ENDOCRINOLOGICAL PERSPECTIVES

Shodmonov Sardor Qahranom o'g'li
EMU University, Tashkent, Uzbekistan

Tangirova Dildora Xusniddin qizi
EMU University, Tashkent, Uzbekistan

Abstract

Diabetic polyneuropathy (DPN) is the most prevalent and disabling chronic complication of diabetes, greatly increasing the risks of foot ulceration, amputation, and cardiovascular morbidity. Traditional treatment—primarily focused on glycemic control and symptomatic pain relief—has shown limited ability to reverse or halt the progression of neuropathy. This review highlights the need for a modern, integrated therapeutic strategy that combines optimized endocrinological management with innovative, pathogenesis-targeted neurological interventions. We explore recent systemic advances, including the metabolic benefits of newer antidiabetic agents such as SGLT2 inhibitors and GLP-1 receptor agonists, as well as the importance of addressing cardiovascular risk factors that contribute to nerve ischemia. Additionally, we discuss emerging disease-modifying therapies, including alpha-lipoic acid, VM202 gene therapy, and high-frequency spinal cord stimulation (SCS). Early detection methods such as Corneal Confocal Microscopy offer promising potential for identifying neuropathy before irreversible damage occurs. A comprehensive, personalized treatment strategy uniting metabolic optimization with advanced neurological therapies offers the greatest opportunity to achieve meaningful clinical improvement and enhance quality of life for patients with DPN. [1]

Keywords: Diabetic Polyneuropathy, Metabolic Dysfunction, Neuroinflammation.

Introduction

Diabetic polyneuropathy (DPN), particularly the common form known as distal symmetrical polyneuropathy (DSPN), affects up to half of individuals with long-standing diabetes and represents a major global health burden. As DPN progresses, patients may develop sensory loss, motor dysfunction, and chronic neuropathic pain (Painful DPN), making it one of the leading causes of non-traumatic lower-limb amputation.[2] The complexity of DPN arises from its dual origin. The endocrinological component involves chronic hyperglycemia, insulin resistance, and dyslipidemia, which initiate metabolic disturbances leading to nerve injury.[3] The neurological component relates to axonal degeneration, impaired nerve conduction, and central sensitization that produces neuropathic pain.[4] Historically, clinical practice relied on two strategies: (1) intensive glycemic reduction and (2) symptomatic pain management. However, this fragmented approach often failed due to “metabolic memory”—the persistence of early

nerve damage despite later glycemic control—and the limited effectiveness of conventional analgesics. This review synthesizes current evidence supporting a modern, integrated treatment paradigm. By addressing both the metabolic roots and neurological consequences of DPN, a combined approach holds the greatest potential to improve outcomes.

The Endocrine–Neurological Nexus: Updated Pathophysiological Insights

Understanding how chronic metabolic dysfunction leads to nerve injury is essential for modern therapy. Hyperglycemia, insulin resistance, and dyslipidemia drive several interconnected biochemical pathways that culminate in oxidative stress, neuroinflammation, and microvascular compromise.[5]

The Initiating Metabolic Pathways. Hyperglycemia drives four major pathways that contribute to DPN pathology:

1. Polyol Pathway Flux: Increased glucose shunted through the aldose-reductase enzyme consumes NADPH and generates osmotically active sorbitol and fructose leading to Schwann cell damage and reducing the available resources for glutathione synthesis (the cell's major antioxidant).[6][7][9][10]
2. Advanced Glycation End-Products (AGEs). Glucose reacts with proteins and lipids to form AGEs, which bind to RAGE receptors on neurons, endothelial cells, and Schwann cells. This triggers inflammatory signaling and vascular impairment.[11][12]
3. Protein Kinase C (PKC) Activation. Hyperglycemia increases diacylglycerol (DAG) levels, activating PKC isoforms that disrupt blood flow regulation and contribute to microvascular damage.[14]
4. Hexosamine Pathway Flux. This pathway modifies proteins through aberrant glycosylation, altering cellular function and contributing to inflammation.[14]

Oxidative Stress and Neuroinflammation. These pathways converge to generate reactive oxygen and nitrogen species, overwhelming antioxidant defenses and damaging neuronal membranes, proteins, and DNA. Simultaneously, AGE-RAGE activation and microvascular ischemia stimulate glial and macrophage-mediated release of pro-inflammatory cytokines such as TNF- α and IL-6. Interrupting this cycle is a major focus of emerging therapies.

Endocrinological Foundations: Glycemic and Metabolic Optimization

The foundation of DPN treatment remains the mitigation of systemic metabolic risk factors. Modern endocrinology provides nuanced strategies beyond simple HbA1c targets.

Targeted Glycemic Control: While intensive blood glucose control is definitively proven to prevent DPN development in Type 1 Diabetes (T1DM), its efficacy in reversing established DPN is limited. However, two modern approaches refine this principle:

Glucose Variability (GV): Recent evidence suggests that high glucose variability (rapid swings in blood glucose), independent of mean HbA1c, may be a stronger predictor and driver of DPN pathology.[15][16] This necessitates the use of modern monitoring tools, such as Continuous Glucose Monitoring (CGM), to stabilize glucose levels and minimize GV.

SGLT2 Inhibitors and GLP-1 Receptor Agonists: Beyond their glucose-lowering effects, these newer anti-diabetic agents may exert neuroprotective benefits.[17] SGLT2 inhibitors improve

microvascular perfusion and reduce inflammation, crucial for nerve health. GLP-1 RAs have shown pleiotropic effects, including potential reduction in neuroinflammation and improvement in nerve blood flow in animal models, supporting their role in a modern DPN management regimen.[18]

Systemic Risk Factor Management. The integrated approach demands aggressive *nervorum*). Hypertension and Dyslipidemia: High blood pressure and dyslipidemia independently accelerate microvascular damage and nerve ischemia. Treating hypertension with ACE inhibitors or ARBs and dyslipidemia with statins is critical. A modern approach views DPN as a systemic vascular disease with neurological consequences, where cardiovascular risk management is neuroprotective.

Insulin and C-peptide: While insulin resistance is central to T2DM, C-peptide, a co-secreted component of insulin, has been studied for its neurotrophic properties. Though not yet a standard therapy, ongoing research explores its potential to improve nerve function, particularly in T1DM.

Neurological Strategies: Disease-Modifying and Symptomatic Therapies

Pathogenesis-Targeted (Disease-Modifying) Therapies. These agents directly address the molecular defects within the nerve, representing the pinnacle of "modern approaches."

Alpha-Lipoic Acid (ALA): This potent mitochondrial antioxidant remains the most well-studied pathogenesis-targeted agent. Meta-analyses consistently demonstrate that intravenous ALA can improve positive neuropathic symptoms (like burning pain and paresthesias) and, in some studies, improve nerve conduction velocities.[19] Oral ALA is used for maintenance, though its efficacy is more variable.

Gene Therapy (VM202): VM202 is an engineered plasmid encoding two isoforms of the human Hepatocyte Growth Factor (HGF).[20] When injected intramuscularly, HGF is theorized to promote angiogenesis, repair damaged nerve cells, and provide neurotrophic support. Pivotal Phase III trials have demonstrated sustained, statistically significant improvements in pain relief and potential functional improvement for up to 12 months, positioning it as a potentially groundbreaking disease-modifying therapy.

Emerging Molecular Targets: Future therapies are exploring the modulation of the Aldose Reductase enzyme with new inhibitors that overcome the failures of earlier agents. Furthermore, research into the link between the Gut Microbiota and DPN suggests that targeted manipulation of intestinal flora may alter the production of inflammatory metabolites that impact nerve health.[20]

Symptomatic Pain Management. Painful DPN (PDN) requires a structured, multi-drug approach. Recent guidelines emphasize combining agents based on mechanism and side-effect profile.

First-Line Pharmacotherapy: Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs): Duloxetine is highly effective, offering the dual benefit of pain reduction and treatment of associated depression and anxiety.[18]

Gabapentinoids: Pregabalin and Gabapentin remain cornerstones of treatment, acting by binding to the α_2 - δ subunit of voltage-gated calcium channels, thereby reducing the release of

excitatory neurotransmitters.[13][14] Newer agents like Mirogabalin aim to improve binding specificity and reduce common side effects like sedation and dizziness.[15]

Second-Line and Interventional Options: Topical Agents: The high-concentration (8%) capsaicin patch provides localized, long-lasting pain relief by defunctionalizing C-fibers via TRPV1 receptor activation. This is a valuable option for localized, refractory pain.[6][7]

Neuromodulation: Spinal Cord Stimulation (SCS): SCS has emerged as a transformative treatment for severe, refractory PDN.[18] High-frequency (10-kHz) SCS has shown significant clinical efficacy in randomized controlled trials, providing substantial pain relief that often surpasses traditional medical management.[19] SCS is believed to act both by altering central pain processing and potentially by improving blood flow to the nerve tissue, making it a powerful integrated neurological intervention.

Conclusion

Management of Diabetic Polyneuropathy is shifting from a reactive, symptom-centered model toward an integrated, mechanism-based approach. Endocrinological strategies are expanding beyond HbA1c to include glucose variability, lipid management, and advanced antidiabetic therapies with neuroprotective potential. Concurrently, neurological interventions are evolving from traditional symptomatic agents to genuine disease-modifying therapies and innovative interventional techniques such as gene therapy and high-frequency SCS. A personalized treatment plan that unites metabolic control with advanced neurological therapies offers the most promising path toward meaningful improvement in patient outcomes and quality of life.

References

1. American Diabetes Association. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2024. *Diabetes Care*. 2024;47(Suppl 1):S209-S218.
2. Gore M, et al. AAN Guideline Update: Oral and Topical Treatment of Painful Diabetic Polyneuropathy. *Neurology*. 2022;98(3):e196-e211.
3. Jardine J, et al. Global prevalence of diabetes-related neuropathies: a systematic review and meta-analysis. *Diabetologia*. 2023;66(5):985-996.
4. Vinik AI, et al. The Pathophysiology of Diabetic Neuropathy. *Gland Surgery*. 2020;9(Suppl 1):S75-S87.
5. Avogaro A, et al. SGLT2 inhibitors and GLP-1 receptor agonists in diabetic neuropathy: mechanisms and clinical perspectives. *Nat Rev Endocrinol*. 2024;20(3):145-159.
6. Xu Y, et al. Glycemic variability is associated with diabetic peripheral neuropathy: A systematic review and meta-analysis. *J Diabetes Complications*. 2021;35(3):107843.
7. Mijnhout GS, et al. alpha-lipoic acid in the treatment of diabetic polyneuropathy: a meta-analysis. *Diabet Med*. 2023;40(6):e15097.
8. Pappas K, et al. VM202 gene therapy for painful diabetic neuropathy: A Phase 3 randomized controlled trial. *Lancet Diabetes Endocrinol*. 2024 (In Press/Trial Data).
9. Oates PJ, et al. Aldose Reductase Inhibitors: Bridging Bench to Bedside in Diabetic Complications. *Trends Pharmacol Sci*. 2020;41(1):16-29.

10. Salsano E, et al. Neurotrophic factors for the treatment of diabetic neuropathy: A systematic review. *J Peripher Nerv Syst.* 2021;26(1):15-28.
11. Gliner N, et al. High-frequency 10 kHz spinal cord stimulation for painful diabetic neuropathy: 24-month results from a randomized controlled trial.³¹ *Diabetes Care.* 2023;46(8):1570-1578.
12. Petersen EA, et al. Spinal Cord Stimulation: A Review of Current Practice and Future Directions. *Pain Pract.* 2022;22(2):123-138.
13. Wiffen PJ, et al. Gabapentinoids and tricyclic antidepressants for neuropathic pain: an overview of Cochrane reviews. *Cochrane Database Syst Rev.* 2021;6(6):CD013824.
14. Kitasato L, et al. Efficacy and safety of mirogabalin for the treatment of painful diabetic peripheral neuropathy: a phase 3 randomized, double-blind study. *Pain.* 2020;161(1):157-167.
15. Simpson DM, et al. Treatment of painful diabetic neuropathy with the Capsaicin patch: a randomized, double-blind, placebo-controlled trial. *JAMA Neurol.* 2020;77(10):1241-1249.
16. Tavakoli M, et al. Corneal Confocal Microscopy: A Novel, Non-Invasive Technique for Diagnosing and Monitoring Human Diabetic Neuropathy. *Trends Endocrinol Metab.* 2021;32(7):448-460.
17. Lu J, et al. Metabolomic analysis of painful and painless diabetic peripheral neuropathy: potential biomarkers. *Mol Pain.* 2023;19:17448069231154563.
18. Ding X, et al. Role of the gut microbiota in the development of diabetic neuropathy. *Front Endocrinol (Lausanne).* 2022;13:1016692.
19. Tesfaye S, et al. Diabetic Neuropathy: Clinical Features and Therapeutic Perspectives. *Diabetes Res Clin Pract.* 2022;184:109156.
20. Pop-Busui R, et al. Diabetic Neuropathy: A Consensus Report From the American Diabetes Association. *Diabetes Care.* 2017;40(1):136-154.