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REVIEW

Promising Biomarkers for Early Diagnosis: Advances in Understanding the Pathogenesis of Diabetic Peripheral Neuropathy

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Abstract: Diabetic peripheral neuropathy (DPN) is one of the most common chronic complications of diabetes mellitus. The most common type is distal symmetric polyneuropathy, and lesions frequently lead to disabling neuropathic pain and even amputation, increasing the risk of death. At present, the pathogenesis of DPN has not been clarified, and its insidious onset and lack of obvious symptoms in most patients in the early stages often lead to delayed diagnosis, which is unfavourable for prevention and treatment. This article provides an overview of the existing research progress on early diagnostic markers of DPN, especially oxidative stress-related markers, neural tissue damage markers, inflammation-related markers, neurovascular damage markers, and gene-related markers, in the hope that it can provide a reference for early diagnosis and treatment of DPN, and slow down the occurrence and development of DPN.

Keywords: diabetic peripheral neuropathy, diagnostic markers, pathogenesis, diabetes mellitus

Introduction

More than 50% of people with diabetes will develop diabetic neuropathy, which is one of the most common and troublesome complications of both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).[1–3] Approximately 30%~40% of patients with diabetic neuropathy report experiencing neuropathic pain, and the main neuropathy is diabetic peripheral neuropathy (DPN).[3,4] DPN is a primary contributor to diabetic foot complications, including ulceration and Charcot neuroarthropathy, often leading to debilitating neuropathic pain and lower-limb amputation.[1,3,5]

According to the World Health Organisation, lower limb amputations are 10 times more common in diabetics than in non-diabetics. Many studies have shown a substantial increase in mortality among diabetics who undergo major amputations, with 5-year mortality rates ranging from 44% to 68%.[1,3] Patients with DPN also have a significantly higher risk of cardiovascular death than those without DPN. The International Diabetes Federation 2021 report identifies diabetes as a fast-growing global epidemic in the 21st century, with an estimated prevalence rising from 10.5% (536.6 million people) in 2021 to 12.2% (783.2 million) in 2045.[3,6,7]

The clinical underdiagnosis of DPN stems from its heterogeneous pathogenesis and symptom overlap with other disorders.[3,4] This diagnostic challenge underscores the urgent need for novel biomarkers. Furthermore, over 50% of DPN patients remain asymptomatic, which further delays early detection. To mitigate the clinical and socioeconomic burden of DPN, identifying reliable diagnostic markers is critical for enabling early screening and intervention. In this article, we summarize the latest research progress on diagnostic markers for DPN in terms of its pathophysiology as well as the mechanisms by which it may occur, expanding new ideas for the prevention and treatment of DPN.

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Pathophysiology of Diabetic Peripheral Neuropathy

DPN pathophysiology involves multifactorial mechanisms, including metabolic dysregulation, mitochondrial dysfunction, and structural nerve damage. The length-dependent lesion of peripheral nerves in DPN occurs first in the toes and progresses to the proximal end. In advanced stages, similar damage may affect the fingers. This nerve damage reflects a "stocking-glove" distribution (Figure 1a), which is closely related to the structure and function of the peripheral nervous system (PNS).[2,3,8]

Peripheral nerves are composed of neurons (cell bodies and axons), supporting glial cells (eg, Schwann cells, SCs), blood vessels, and connective tissues. Each sensory axon (nerve fibre) extends from a dorsal root ganglion (DRG) neuron and usually carries electrical impulses. Sensory and motor neurons transmit afferent and efferent signals through nerve fibers, which are classified as unmyelinated (eg, C fibers) or myelinated (eg, Aδ and Aβ fibers), enabling distinct sensory modalities and conduction velocities.[8] Under diabetic conditions (eg, hyperglycemia and dyslipidemia), neural structure is disrupted, accompanied by bioenergetic deficits, impaired insulin signaling, inflammation, oxidative stress, microvascular damage (Figure 1b). These are the typical pathological features of DPN.[8–10]

Long axons in the limbs require substantial energy to maintain membrane potential and signal transmission, primarily sourced from substrate catabolism via metabolic coupling between SCs and axons. SCs preferentially utilize glucose through glycolysis for adenosine triphosphate (ATP) production, with alternative pathways (eg, fatty acid oxidation) contributing to energy supply. Additionally, bidirectional communication between neurons and SCs occurs via paracrine signaling, extracellular vesicles, and direct molecular exchange.[2,8] At the cellular level, mitochondrial dysfunction and oxidative stress in SCs drive neuronal damage, including axonal loss and demyelination, ultimately impairing energy homeostasis (Figure 2).[9] Notably, insulin signaling—particularly through the PI3K-Akt pathway—plays a dual role: it

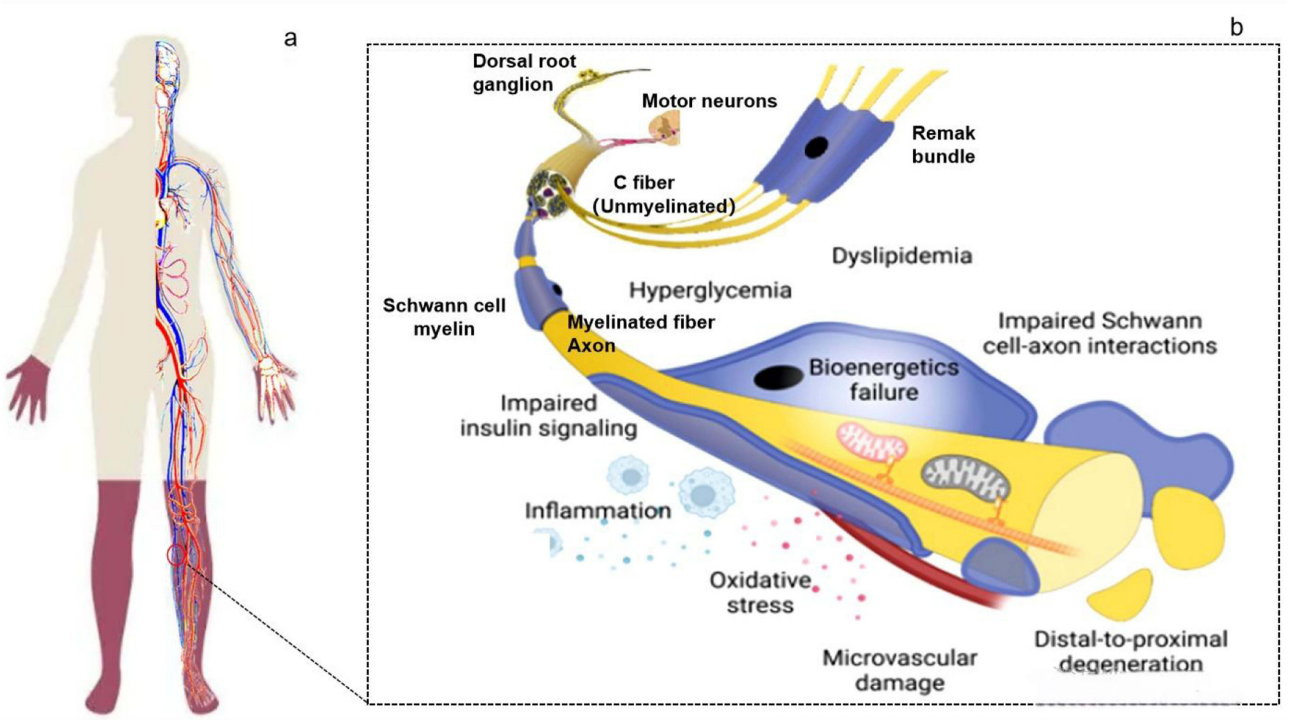

Figure 1 PNS structure and pathophysiology of diabetic peripheral neuropathy.[2,8] (**a**) DPN manifests as nerve injury (red color) in a "stocking-glove" pattern. (**b**) Sustained hyperglycemia triggers oxidative stress and inflammation via the polyol pathway, advanced glycation end-products (AGEs) accumulation, and mitochondrial dysfunction, collectively damaging neurons and glial cells. Schwann cells (SCs)-critical for myelination-exhibit impaired interactions with axons, a hallmark of DPN. Hyperglycemia disrupts SC metabolic homeostasis, causing myelin sheath abnormalities and demyelination of myelinated fibers. It also alters the microenvironment of unmyelinated C-fibers in Remak bundles, promoting degeneration of sensory neurons (eg, dorsal root ganglia) and motor neurons. Inflammatory mediators and oxidative stress further impair axonal transport and and endoneurial blood flow, ultimately leading to pain, paresthesia, and motor deficits. The pathogenic complexity of DPN, rooted in multifactorial interactions, offers actionable insights for precision diagnosis and therapy.

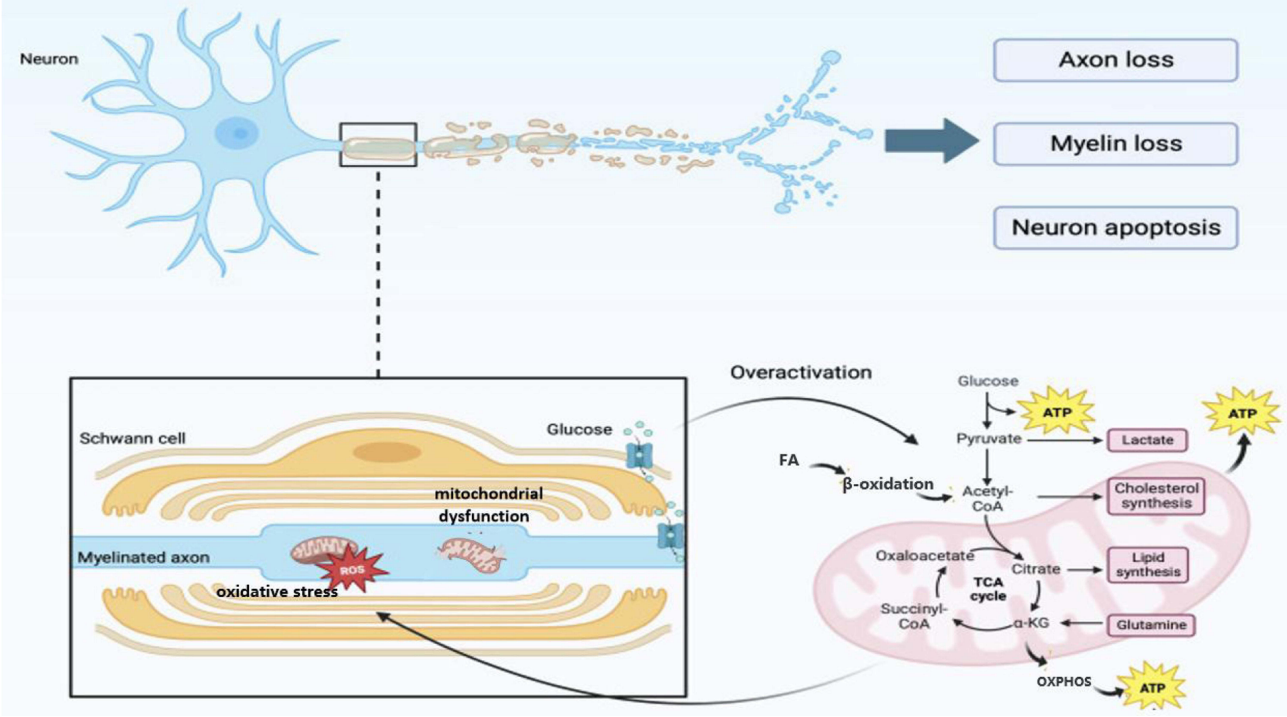

Figure 2 Demyelination and axonal damage of DPN.[8,9] Energy production in Schwann cells (SCs) relies on substrate catabolism to generate ATP. Glucose is preferentially metabolized via glycolysis to pyruvate, which enters mitochondria through the mitochondrial pyruvate carrier (MPC). Pyruvate fuels the tricarboxylic acid (TCA) cycle, providing substrates for oxidative phosphorylation (OXPHOS) in the inner mitochondrial membrane (IMM). Fatty acid oxidation (FAO) serves as an alternative energy source. SCs also synthesize cholesterol and lipids critical for myelin maintenance. Bidirectional communication between neurons and SCs occurs via paracrine factors (eg, growth factors), gap junctions, and extracellular vesicles (EVs) carrying miRNAs. In DPN, hyperglycemia disrupts SC-axon metabolic coupling, impairing mitochondrial function and ATP synthesis. Concurrently, oxidative stress and TCA cycle dysfunction (eg, altered succinyl-CoA and oxaloacetate levels) exacerbate demyelination and axonal loss. These metabolic deficits misprocessing, drive a degenerative cascade characterized by neuronal apoptosis and motor-sensory deficits.

not only regulates glucose metabolism but also promotes SC differentiation and remyelination, thereby mitigating DPN progression.[9,11–13]

DPN induces progressive sensory fiber degeneration and neuropathic pain, mediated by voltage-gated sodium channel (VGSC; $Na_v1.7$, 1.8),[8] voltage-gated potassium channels, ligand-gated transduction channels (eg, transient receptor potential cation channel subfamily A member 1, (Nav1.8, TRPA1),[14] calcium channels (CAV3.2), and hyperpolarization-activated cyclic nucleotide-gated channels (HCN2).[2]

In healthy neural states (Figure 3a and b), ion channels sense initial stimuli and transmit them to sensory receptors.[2] Subsequently, neural ion channels generate an action potential, which propagates along the axon to the central nervous system (CNS). Finally, in the dorsal horn of the spinal cord, ion channels trigger the release of neurotransmitters, at which time the potential changes of nerve membranes are relatively stable, and nerve cells produce ATP through normal energy metabolism to maintain cell function. Nav1.8 and TRPA1 channels also play a normal role.

However, in DPN (Figure 3c and d), mutated Nav1.7 and 1.8 channels cause abnormal oscillations in nerve membrane potential. At the same time, TRPA1 is modified by methylglyoxal, which triggers a series of changes, including increased production of reactive oxygen species (ROS), blocked production of ATP, and inflammatory responses. Glucose transporter 3 (GLUT3) function may also be affected, with abnormal glucose (GLU) metabolism in nerve cells. These changes are closely related to the mechanism of abnormal nerve signals and nerve damage in diabetic peripheral neuropathy.[8]

Hyperglycemia and hyperlipidemia disrupt nerve function via multiple pathways,[9] including protein kinase C (PKC) pathway, polyol pathway, advanced glycosylated terminal (AGE) pathway, hexosamine pathway, PARP pathway, insulin pathway, compounded by mitochondrial dysfunction, oxidative stress, inflammatory response, metabolic abnormalities,

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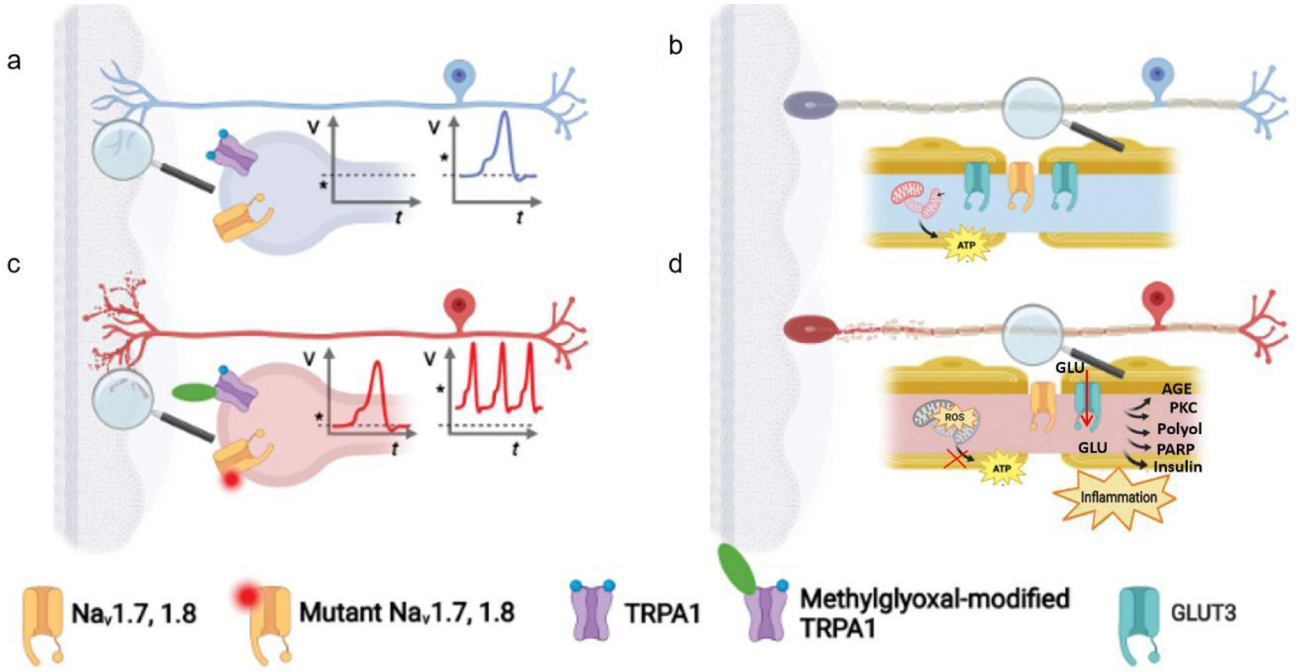

Figure 3 Neuropathy of diabetic peripheral neuropathy.[2,9] (**a**) Under normal circumstances, the changes of nerve cell membrane potential are relatively stable; (**b**) nerve cells produce ATP through normal energy metabolism to maintain cell function, and TRPA1 ion channels play a normal role. (**c**) DPN reaction substrate and channel changes involve a variety of molecules related to nerve conduction, such as mutated Nav1.7 and 1.8 channels that cause abnormal oscillation of nerve cell membrane potential, methylglyoxal modifies TRPA1 to change its function and participate in the neuropathic process. (**d**) GLUT3 (glucose transporter 3) function may also be affected, further affecting D-glucose uptake and metabolism of nerve cells, glucose (GLU) metabolism is abnormal, reactive oxygen species (ROS) production is increased, mitochondrial function is affected, and ATP production is blocked. At the same time, a series of signaling pathways are activated, such as AGE (advanced glycosylation end products) -PKC (protein kinase C) pathway, Polyol pathway, PARP (polyADP-ribose polymerase) pathway, leading to inflammation.

and microvascular disease.[15,16] Neuronal demyelination and neuronal damage (Figure 3c and d) ultimately slows down nerve conduction, which in turn leads to energy loss and metabolic disorders.[8]

In light of the established pathophysiological mechanisms outlined in previous sections, we systematically evaluate existing diagnostic modalities for DPN and propose novel biomarkers that may enhance early detection and clinical management.

Electrophysiological Diagnosis of Neuropathy

Electrophysiological Indicators

The clinical diagnosis of DPN requires identification of neuropathy signs/symptoms in patients with prediabetes or diabetes mellitus following exclusion of alternative etiologies.[4,6,17] Initial evaluation combines medical history, symptom analysis, and physical examination. Electrophysiological testing becomes essential for atypical presentations, with nerve conduction studies (NCS) remaining the diagnostic gold standard.[1,18–20] To enhance diagnostic completeness, composite indices that integrate symptoms, signs, and simple tests are invaluable. For instance, the DPN-Check is a succinct, patient-administered screening tool that efficiently combines symptom questionnaires with monofilament and vibration perception tests, offering a rapid clinical assessment. In contrast, the more comprehensive Toronto Clinical Neuropathy Score (TCNS) systematically grades symptoms, sensory test results, and reflex outcomes to quantify both the presence and severity of DPN. The inclusion of such indices provides a structured, multi-modal framework that complements single biomarker findings and aligns with holistic diagnostic approaches.

NCS serve as the cornerstone of electrophysiological diagnostics, evaluating conduction abnormalities in both sensory (eg, sural and superficial peroneal nerves) and motor nerves (eg, tibial and common peroneal nerves) to assess axonal integrity and demyelination in diabetic neuropathy. Clinically, we commonly use electrical diagnostic tests (eg, electromyography, EMG),[21–25] which mainly investigate NCS and F-wave abnormality rate or other abnormal parameters, to confirm the severity of nerve damage. NCS combined with F-wave analysis demonstrates high diagnostic

accuracy (sensitivity, specificity >80%).[25] Patients with extended disease duration (>10 years) exhibited markedly slower motor nerve conduction velocities (NCV) in the median, ulnar, common peroneal, and posterior tibial nerves compared to those with early-stage disease (<1 year)[23] accompanied by progressive amplitude reduction.[2]. This temporal decline in neural function is further corroborated by preclinical evidence: diabetic animal models demonstrated a 44.4% decrease in mean NCV versus non-diabetic controls (P<0.001).[26] Integration of HbA1c values with electromyography enhances early detection (98% sensitivity, 94% specificity).[24] Significantly, combining NCS with clinical examination increases diagnostic yield from 40.4% to 62.2%, with 14.0% prevalence of neuropathic pain.[27] The evidence suggests NCS parameters may serve prognostic functions, as demonstrated by improved conduction velocities following 6–12 weeks of statin therapy.[28,29]

Conventional nerve conduction studies primarily assess large-fiber neuropathy;[2] however, DPN predominantly involves pathologies of small myelinated and unmyelinated nerve fibers, which are critical for nociceptive signal transmission in response to noxious stimuli. Particularly, standard electrophysiological modalities such as NCV testing and EMG exhibit limited sensitivity in detecting small-fiber dysfunction,[29] particularly in asymptomatic patients or those with early-stage DPN characterized by subclinical neuropathic alterations.

Small-Fiber Neuropathy (SFN) Diagnostics

Small-fiber neuropathy (SFN), a pivotal contributor to neuropathic pain and a hallmark of early diabetic peripheral neuropathy (DPN),[30,31] presents significant diagnostic challenges due to the limited sensitivity of conventional nerve conduction studies (NCS) in detecting small myelinated and unmyelinated fiber pathology.[32] To address NCS utility is constrained in detecting SFN, skin biopsy with intraepidermal nerve fiber density (IENFD) quantification has emerged as a complementary diagnostic modality, demonstrating high diagnostic efficacy (88%), positive predictive value (75%), and negative predictive value (90%) for neuropathy.[33] Of note, IENFD shows superior sensitivity (51.1%; 95% CI: 43.7–58.5) and specificity (90%; 95% CI: 79.5–96.2) for early SFN detection compared to conventional electrophysiological methods.[34] Despite these advantages, IENFD faces criticism due to its reduced sensitivity in identifying mild nerve damage and the inherent challenges in tracking longitudinal neural changes, underscoring the need for more refined quantitative methodologies to enhance its clinical applicability.[35] Moreover, skin biopsy is invasive, expensive and lacks diagnostic laboratory capacity.[36] These limitations highlight the importance of integrating multimodal diagnostic approaches to optimize SFN assessment and monitoring.

In recent years, corneal confocal microscopy (CCM) has assessed non-invasive assessment of small-fiber integrity.[34,36–38] By leveraging high-resolution confocal imaging, CCM enables precise quantification of corneal subepithelial nerve plexus morphology—including nerve fiber length, density, branching complexity, and curvature[39]—providing a surrogate marker for peripheral small-fiber damage in DPN.[31] This conclusion is corroborated by a meta-analysis of 13 studies involving 1680 participants, which confirms the diagnostic utility of CCM in detecting early neural degeneration in DPN.[40] This technique not only correlates strongly with IENFD but also facilitates dynamic monitoring of neuropathic progression and therapeutic response.[34] CCM provides high-resolution structural assessment of the corneal subepithelial nerve plexus, its utility is restricted to localized evaluation of small-fiber morphology and does not extend to systemic small-fiber pathology. Furthermore, diagnostic interpretation of CCM findings requires careful exclusion of confounding ocular comorbidities (eg, dry eye syndrome, infectious keratitis), as these conditions may artifactually alter nerve architecture and compromise specificity.

Parallel advancements in functional assessments include quantitative sensory testing (QST), which evaluates nociceptive thresholds (eg, thermal and mechanical pain sensitivity).[31] Nociceptive hypersensitivity, reflecting early small-fiber dysfunction, exhibits high diagnostic accuracy (sensitivity: 84%; specificity: 81%),[41] positioning QST as a valuable tool for identifying subclinical DPN. Although the subjectivity of Quantitative Sensory Testing (QST) is well-recognized, emerging automated thermal threshold testing devices enhance objectivity by standardizing stimulus delivery and response recording.

The comparative strengths and limitations of these diagnostic modalities are summarized in Table 1. While current methods demonstrate clinical utility in detecting DPN across disease stages, their inherent constraints—including invasiveness, operator dependency, and limited sensitivity for early small-fiber pathology—highlight the urgent need

Table 1 Assessing Clinical Detection Method in DPN (Human Clinical Study)

Detection Method	Assessed Fiber Type	Advantages	Limitations
CCM	Small fibers (structural)	Non-invasive, high resolution, early diagnosis	Cannot assess large fiber function
IENFD	Small fibers (structural)	Gold standard	Invasive, technically complex
QST	Small fibers (functional)	Evaluates abnormal pain/thermal sensation	High subjectivity
NCV/EMG	Large fibers (functional)	Identifies conduction velocity abnormalities	Insensitive to early small fiber pathology

to develop and validate novel non-invasive biomarkers with enhanced specificity for neuroaxonal degeneration. Future research should prioritize translational innovations to bridge this diagnostic gap and refine precision medicine strategies in DPN management.

Neurotissue Damage Factor (NTDF)

Neurofilament Heavy Chain (NF-H)

Emerging biomarkers for small-fiber neuropathy (SFN) highlight axonal degeneration as a critical early pathological feature.[42] Neurofilament heavy chain (NF-H), a cytoskeletal protein essential for axonal integrity, undergoes phosphorylation (pNF-H)—a post-translational modification regulating axonal caliber and microtubule interactions. Serum pNF-H exhibits exceptional stability, resisting enzymatic degradation, and serves as a robust biomarker of neuroaxonal injury. Preclinical studies demonstrate that restoring NF homeostasis rescues neuronal ultrastructure and immunohistochemical signatures in diabetic models.[43] Clinically, pNF-H levels are elevated in diabetic peripheral neuropathy (DPN) patients (605.99 [IQR: 281.17–1332.78] pg/mL) versus non-DPN controls (311.98 [189.59–634.12] pg/mL; $P = 0.007$),[44] with impaired glucose tolerance (IGT)-SFN subgroups showing intermediate elevations (170.6 [140.0–223.6] pg/mL vs controls: 76.55 pg/mL, IGT-non-SFN: 64.7 pg/mL).[32] Multivariate analysis identifies pNF-H (OR = 1.429, 95% CI: 1.315–1.924) and 2-hour plasma glucose (OR = 2.375, 1.157–4.837) as independent SFN predictors,[32], establishing pNF-H as a type 2 diabetes-specific risk marker. Prospective validation of its prognostic utility and therapeutic targeting potential is warranted.

Myelin Protein Zero (MPZ)

A prospective observational pilot study[3] revealed a novel link between myelin-associated protein mutations and neurodegeneration in DPN. In human Schwann cells and nerve tissue biopsies, myelin protein zero (MPZ) emerged as the most robust biomarker of myelin integrity. Participants with DPN exhibited a marked reduction in circulating MPZ mRNA levels ($P < 0.001$) alongside elevated serum neurofilament light chain (NFL) protein concentrations ($P<0.05$). Participants with DPN exhibited a marked reduction in circulating MPZ mRNA levels (quantified by qRT-PCR; $P < 0.001$) alongside elevated serum neurofilament light chain (NFL) protein concentrations (measured via a high-sensitivity immunoassay; $P < 0.05$). These alterations correlated significantly with electrophysiological abnormalities, diminished fractional anisotropy on diffusion tensor imaging, and quantitative sensory testing deficits. Longitudinal analysis demonstrated that elevated NFL levels predicted pain hypersensitivity phenotypes ($P<0.05$), while reduced MPZ mRNA preceded pain alleviation ($P<0.001$) and heralded progressive nerve dysfunction 24 months in advance (hazard ratio [HR] = 6.519). These findings position NFL and MPZ mRNA as dual biomarkers for distinguishing axonal degeneration (associated with hyperalgesia) from demyelination (linked to hypoalgesia), offering a mechanistic framework for phenotype-specific diagnosis in DPN. The biological rationale for the inclusion of NF-H and MPZ is based on their distinct structural properties: NF-H, as a heavily phosphorylated and cross-linked cytoskeletal component of axons, exhibits remarkable protease resistance and an extended half-life in circulation following axonal injury, while MPZ, as a key structural protein of myelin, is released into serum upon demyelination, with its detection window influenced by its comparatively shorter half-life.

Nerve Growth Factor (NGF)

Axonal degeneration in DPN is mechanistically linked to diminished nerve growth factor (NGF) expression,[29,45] driven by microcirculatory impairment and hypoxia-ischemia-induced neuronal injury.[46] Beyond its well-established roles in

promoting angiogenesis and peripheral nerve repair,[47] NGF critically protects against SC apoptosis,[48] and sustains the functional integrity of DRG sensory neurons-a dual mechanism essential for mitigating DPN progression.[49] A clinical study has further validated the diagnostic utility of NGF in DPN. A serum NGF threshold of 50.25 pg/mL demonstrates high diagnostic efficacy, with sensitivity, specificity, and accuracy reaching 96.9%, 77.3%, and 84.6%, respectively.[50] These emerging studies highlight the translational value of NGF-based strategies, offering both therapeutic avenues to attenuate DPN progression and biomarker-driven tools for precision patient stratification. Incorporating comparative data on BDNF or NT-3 would enhance the comprehensiveness of the analysis and help better contextualize the specific role of NGF in diabetic peripheral neuropathy.

Neuron-Specific Enolase (NSE)

NSE, a cytoplasmic glycolytic enzyme predominantly expressed in neuroendocrine and neuronal tissues, is released into systemic circulation following neuronal injury, with a biological half-life of 48 hours.[51] Elevated serum NSE levels reflect neuroaxonal damage and correlate with DPN severity.[52] In clinical cohorts, NSE concentrations were marginally higher in diabetes patients versus controls (9.1 ± 1.5 vs 8.7±1.7 μg/L, P=0.037), but markedly elevated in DPN subgroups compared to non-neuropathic diabetics (10.8 ± 2.8 vs 9.1 ± 1.5 μg/L, $P < 0.001$). At a diagnostic threshold of 10.10 μg/L, NSE achieved 66.3% sensitivity and 72.5% specificity for distinguishing DPN,[51] outperforming heat shock protein 27 (HSP27) in discriminatory capacity (sensitivity: 92% vs 75%; specificity: 74% vs 71%).[53] These findings position NSE as a promising biomarker for neuroaxonal injury in DPN, though therapeutic targeting of NSE-related pathways remains exploratory.

Protein Kinase C (PKC)

PKC, a serine/threonine kinase, mediates bidirectional regulatory effects on neuronal function through its multifunctional signaling pathway. Chronic hyperglycemia promotes glyceraldehyde-3-phosphate accumulation, which is subsequently converted to diacylglycerol (DAG) - a potent activator of neuronal PKC isoforms.[54] This metabolic cascade induces PKC hyperactivation, initiating a pathogenic cascade. Clinically, PKC dysregulation correlates with characteristic DPN symptoms including lower extremity burning pain, paresthesia, and numbness. Preclinical studies establish direct links between PKC signaling and peripheral inflammatory pain pathways,[55,56] potentially mediated through the TGF-β/PKC/TRPV1 axis.[57] Mechanistically, PKC activation reduces Na/K-ATPase activity,[58] disrupting ionic homeostasis and impairing NCV and regenerative capacity.[59] This dysfunction is further exacerbated by upregulated TRPV1-mediated currents, which correlate with clinical manifestations of sensory abnormalities.[60] Therapeutic targeting of this pathway demonstrates clinical promise: PKC inhibitors such as ruboxistaurin significantly restore nerve conduction parameters and microvascular perfusion.[30,61] Especially, PKC-δ emerges as a robust diagnostic biomarker, with serum levels >16.6 achieving 89% sensitivity and 100% specificity for distinguishing diabetic patients with neuropathy.[58] These findings collectively validate PKC-δ dual role as both a pathogenic mediator and a modifiable therapeutic target in diabetic neuropathy.

Despite the availability of alternative diagnostic modalities for nerve injury assessment, most remain validated against NCS as the clinical reference standard. As summarized in Table 2, emerging biomarkers exhibit variable diagnostic performance, with sensitivities ranging from 51.1% to 96.9% and specificities between 67.4% and 100%. But these novel biomarkers are currently confined to preclinical and early-phase clinical research. To advance their translational potential, some critical steps are required: multicenter trials employing standardized protocols to establish population-specific diagnostic thresholds via ROC curve analysis and comparative studies across diverse genetic backgrounds (eg, Asian vs Caucasian cohorts) to address potential biomarker variability in sensitivity (Δ >15% in pilot studies) and specificity.

Oxidative Stress-Related Biomarkers

Oxidative stress has emerged as a pivotal pathophysiological mechanism underlying DPN, characterized by disrupted redox homeostasis resulting from excessive ROS generation and impaired antioxidant defense systems.[64] This imbalance induces oxidative damage through multiple pathways, including neuronal morphological alterations, protein/nucleic acid

Table 2 Sensitivity and Specificity of Diagnostic Markers for Nerve Injury (Human Clinical Study)

Biomarker	Study Population	Biologic Function	Sensitivity (%)	Specificity (%)	Validation Stage
NCS[62]	151 patients with T2DM	Gold standard of DPN	91.5	67.4	Clinical
IENFD[34]	97 healthy control; 214 probable and confirmed; 63 non-DPN	A hallmark of early DPN	51.1 (95% CI: 43.7–58.5)	90 (95% CI: 79.5–96.2)	Clinical
IENFD[63]	84 healthy control; 29 diabetic subjects	A hallmark of early DPN	72.4	76.2	Clinical
pNF-H[32]	33 healthy control; 44 IGT patients (24 IGT- SFN)		–	–	Preclinical
MPZ[3]	Human Schwann cells and nerve tissue biopsies	Mutations in myelination-associated proteins drive neurodegeneration by disrupting myelin integrity.	–	–	Molecular
NGF[50]	100 healthy control; 83 T2 DM (non-DPN) ; 65 DPN	Essential in maturation of synapses, axon targeting, synaptic plasticity, as well as neuron growth	96.9	77.3	Molecular
NSE[51]	136 healthy control; 218 diabetic subjects (non-DPN); 214 DPN	A measure of nerve damage	66.3	72.5	Clinical
NSE[53]	50 healthy control; 38 Children with T1 DM (non-DPN); 12 DPN	A measure of nerve damage	92	74	Clinical
PKC[58]	100 diabetic patients (non-DPN); 100 DPN	Reduces Na^+/K^+-ATPase activity and amplifies TRPV1 correlating with burning pain and paresthesia	89	100	Preclinical

denaturation, and ultimately programmed cell death.[65] Substantial evidence supports oxidative stress as a primary driver of neuronal dysfunction in DPN.[22]

Hyperglycemia-driven ROS overproduction predominantly arises from two mechanisms:[66]

Glucose Autoxidation (animal model, in vitro data): Direct generation of ROS via glucose metabolism intermediates by NOS, NADPH oxidases, xanthine oxidase, and hemeperoxidase enzymes, such as myeloperoxidase;

Non-enzymatic Protein Glycation (animal model, in vitro data): Formation of advanced glycation end-products (AGEs), which amplify oxidative damage through receptor-mediated signaling.

Persistent elevations in ROS and reactive nitrogen species (RNS) contribute to endothelial dysfunction, insulin resistance, and pancreatic β-cell impairment, thereby accelerating both microvascular and macrovascular diabetic complications.[66,67] Preclinical studies using DRG neurons exposed to high-glucose conditions reveal a characteristic oxidative stress profile: 3-fold elevation of lipid peroxidation marker malondialdehyde (MDA), coupled with 60% and 50% reductions in GSH and SOD activity, respectively.[68]

Early clinical investigations confirm these findings in DPN patients:[69]

Compared to healthy controls (human clinical study): Serum MDA levels are elevated by >2-fold (healthy: 0.55 ±0.05 nmol/L vs DPN: 1.35±0.13 nmol/L; $p < 0.01$), with GSH levels reduced by 27.7% ± 2.0% (healthy: 52.45 ± 3.22 mg/dL vs DPN: 37.9 ± 1.18 mg/dL);

Compared to diabetics without DPN (human clinical study): DPN patients exhibit a 1.4-fold increase in MDA (non-DPN: 0.96 ± 0.07 nmol/L vs DPN: 1.35 ± 0.13 nmol/L) and a 3.68% ± 1.68% decline in GSH (non-DPN: 39.35 ± 1.73 mg/dL vs DPN: 37.9 ± 1.18 mg/dL).

A meta-analysis by Mallet et al's meta-analysis of 69 articles[56] further solidifies the role of oxidative stress biomarkers in DPN, establishing two critical associations:

1. Systemic oxidative burden: Total oxidative status (TOS) and oxidative stress index (OSI) are significantly elevated in DPN patients, and
2. Genetic susceptibility: Polymorphisms in antioxidant enzyme genes (eg, glutathione peroxidase, GPx) correlate with increased DPN risk and ROS-induced DNA damage, particularly via hydrogen peroxide-mediated pathways.[70]

The convergence of evidence presented here not only consolidates oxidative stress as a central mediator of neuropathic pathogenesis but also offer operational thresholds and reference ranges to standardize DPN diagnostic workflows. Recent trials highlight the therapeutic potential of targeting oxidative stress:

After-treatment cohorts exhibit significant reductions in MDA levels, restored SOD activity, elevated total antioxidant capacity (TAOC), as well as improved motor/sensory NCVs compared to before-treatment baselines ($P< 0.05$).[71]

Bilirubin (human clinical study): This endogenous antioxidant may mitigate DPN risk by suppressing ROS via inhibition of the PKC-NAD (P)H oxidase pathway.[22]

NRF-2 (animal model, in vitro data): Preclinical experiments also confirmed that it can improve diabetes peripheral neuropathy by activating the NRF-2 dependent antioxidant system.[72–75]

N-acetylcysteine (NAC) (human clinical study): High-dose NAC therapy demonstrates clinical efficacy, increasing NRF2 levels by 25.3% ($p < 0.05$) and glutathione peroxidase (GPx) activity by 100%, while reducing TNF-α levels by 21.45% compared to controls.[76] It is critical to note that the canonical activation of NRF2 predominantly occurs through the kinetic inhibition of its repressor, KEAP1, which involves the covalent modification of specific cysteine residues on KEAP1 by electrophiles, thereby stabilizing NRF2; furthermore, emerging pharmacologic strategies are exploring both covalent and non-covalent KEAP1-NRF2 protein–protein interaction inhibitors, which exhibit distinct kinetic and toxicological profiles.

This study expands the therapeutic effect of DPN under the antioxidant system, which may reduce the structural and functional damage to nerve fibers, thus maintaining the integrity of neurons under the condition of diabetes.

Conversely, methylglyoxal, a cytotoxic glycolysis byproduct and AGE precursor, exacerbates peripheral nerve and Schwann cell damage through oxidative pathways.[77] Intriguingly, methylglyoxal modulates ion channel function (eg, Nav 1.8, TRPA1), potentially linking oxidative stress to painful DPN phenotypes.[8] Mitochondrial dysfunction in Schwann cells (SCs) is not merely an accompanying phenomenon but a central driver of phenotypic transition, myelin maintenance failure, and subsequent axonal degeneration. The hyperglycemic milieu directly impairs SC mitochondrial homeostasis by disrupting critical cellular energy-sensing and metabolic pathways. Dysregulation of the AMPK/PGC-1α signaling axis is considered a pivotal event.[78] PGC-1α can inhibit the dedifferentiation of Schwann cells by targeting paraoxonase 1 (PON1), thereby delaying peripheral nerve degeneration. Activation of the AMPK/SIRT1/PGC-1αpathway can alleviate high glucose-induced oxidative stress, ferroptosis, and mitochondrial dysfunction in Schwann cells.[79] Furthermore, AMPK signaling is involved in regulating mitophagy, the process of clearing damaged mitochondria, which is crucial for maintaining SC health.[80]

Although the mechanism of oxidative stress has been confirmed by many research inferences (Figure 4), there are still key challenges in DPN. The specificity and sensitivity of oxidative stress biomarkers (eg, MDA, GSH, NRF2, methylglyoxal (human clinical study)) require rigorous validation in diverse populations. While preclinical/clinical studies show promise, large-scale human trials are lacking. Genetic polymorphisms caused by oxidative stress will also be a new field, which will be summarized and analyzed in the following content.

Neuro-Vascular Injury Related Markers

DPN is characterized as a symmetrical, length-dependent sensorimotor polyneuropathy resulting from chronic hyperglycemia-associated metabolic derangements that contribute to microvascular dysfunction and cardiovascular

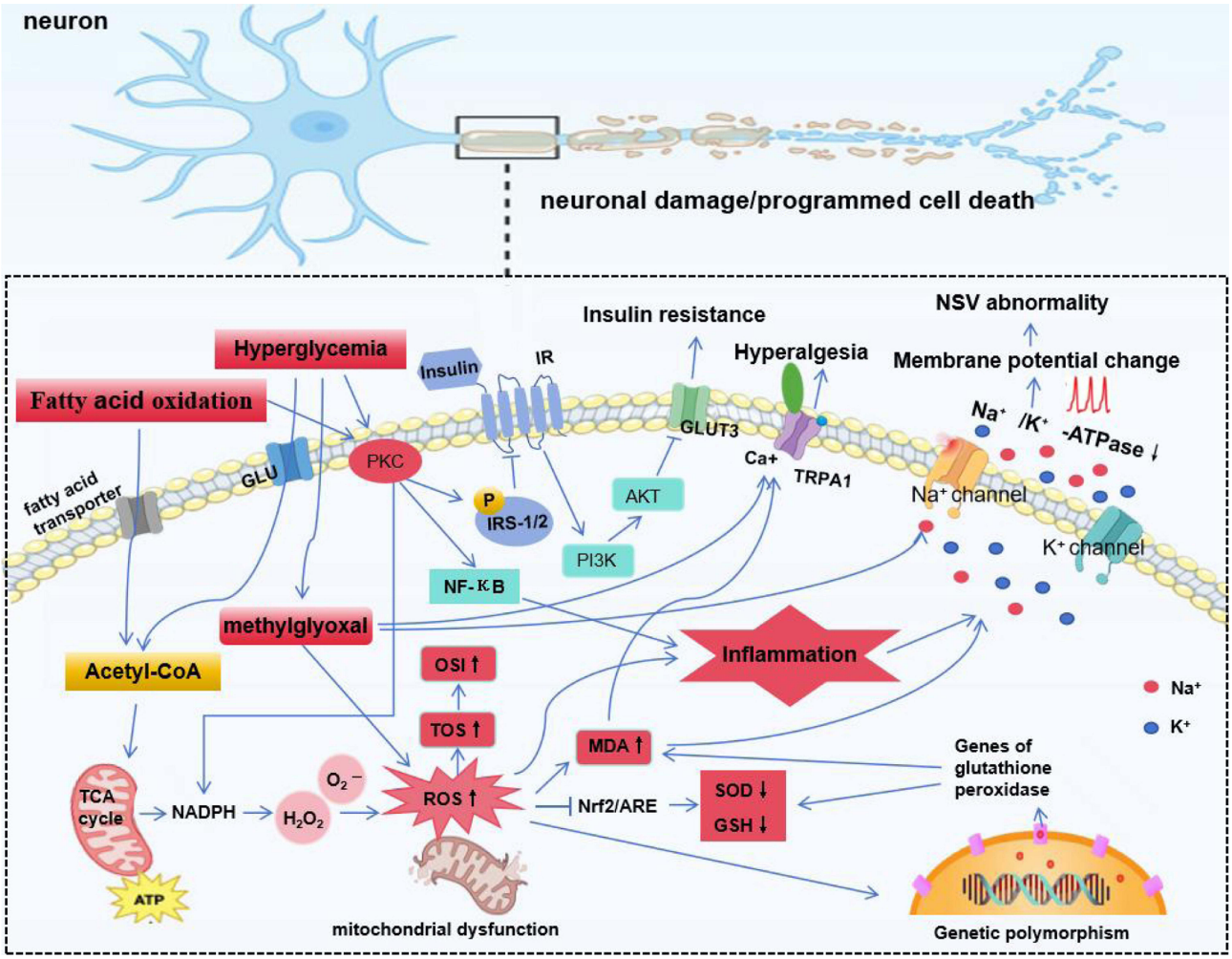

Figure 4 Possible mechanisms and biomarkers of oxidative stress in DPN.[9] Under hyperglycemic conditions, glucose auto-oxidation and non-enzymatic protein glycation impair glycolysis, generating methylglyoxal as a cytotoxic byproduct. Methylglyoxal modulates ion channels (Nav1.8/TRPA1) to induce DPN-associated pain and reduced nerve conduction velocity. Concurrently, hyperglycemia-driven oxidative pathways elevate lipid peroxidation biomarkers (eg, malondialdehyde, MDA), depleting antioxidant defenses (glutathione, GSH; superoxide dismutase, SOD) and exacerbating mitochondrial dysfunction. This dysfunction amplifies superoxide anion and reactive oxygen species (ROS) production, reflected by elevated total oxidative state (TOS) and oxidative stress index (OSI). Hyperglycemia activate protein kinase C (PKC), impairing insulin signaling and promoting insulin resistance. These cascades further increase MDA levels and may influence genetic polymorphisms in antioxidant enzyme-encoding genes (eg, glutathione peroxidase). PKC activation may also affect the production of oxidants and AGEs through the NADPH oxidase complex, causing alterations in cellular functioning. Furthermore, this results in abnormal NSV. The imbalance induces neuronal damage and ultimately programmed cell death. Notably, oxidative stress markers (MDA, TOS, OSI) represent potential early diagnostic indicators for DPN progression.

comorbidities.[6] Cheng et al[4] (human clinical study) systematically demonstrated that cardiac troponin T (cTnT), B-type natriuretic peptide (BNP), C-reactive protein (CRP), myeloperoxidase (MPO), and homocysteine (Hcy) may serve as clinically actionable indicators for early diagnosis and risk stratification of DPN.

Hcy- A Dual Role in Oxidative Stress and Neurotoxicity

Hcy (human clinical study) has emerged as a key mediator of neurovascular injury in DPN, with study analyses confirming its elevated serum levels in patients across diverse populations.[69,81–83] A study revealed a 23% increase in DPN risk per 1 μmol/L increment in plasma Hcy.[84] Consistently, subjects with confirmed DNP exhibited significantly elevated total plasma Hcy levels compared to non-neuropathic controls (12.8 [9.2–14.8] μmol/L vs 8.0 [7.7–9.1] μmol/L, P=0.005), highlighting its potential as a modifiable risk factor in diabetes management.[85] In a retrospective study, patients were divided into two groups based on blood Hcy levels, namely the HHcy group and the NHHcy group. The incidence rates of DPN in both groups were 98.5% and 36.2%, respectively.[82]

Hcy levels >15 μmol/L induce reductions in NCV,[82,86] however, one study reported no significant decrease in tibial NCV despite elevated HCY level.[87] Mechanistically, this discrepancy may arise from differential susceptibility of nerve subtypes, with high Hcy levels driving synergistic pathways:[82,88] (1) oxidative stress, (2) endothelial cell damage, and (3) neurotoxicity damage. While these findings position Hcy as a promising diagnostic candidate, its specificity and sensitivity require validation in multi-ethnic cohorts.

CRP and MPO

Related to inflammation. Elevated levels of CRP and MPO frequently co-occur with pro-inflammatory cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in experimental diabetic neuropathy models[26,89–91] (animal model, in vitro data). Emerging clinical evidence indicates that serum CRP (human clinical study) is significantly increased in patients with DPN,[91–93] while higher CRP level is inversely related to NCV (P<0.001),[91] suggesting a role for systemic inflammation in axonal dysfunction. Preclinical studies associate MPO with behavioral abnormalities, sciatic nerve demyelination, and NCV impairment.[26,90] Clinically (human clinical study), a German prospective cohort established MPO as an independent predictor of DPN progression.[94] These suggest the role of CRP and MPO in bridging oxidative stress, inflammation and neural degeneration.

Cardiac Biomarkers (BNP/NT-proBNP, Hs-cTnT)

BNP/NT-proBNP and hs-cTnT (human clinical study) exhibit strong associations with peripheral neuropathy severity.[95] In T2DM patients, elevated serum BNP correlates positively with systolic blood pressure, neutrophil-to-lymphocyte ratio (NLR), vibration perception thresholds, and comorbidities including diabetic foot ulcers and nephropathy.[96] Furthermore, NT-proBNP levels predict microvascular and macrovascular complication risks in diabetes.[97] This relationship may stem from shared microvascular pathophysiology: impaired neural perfusion in DPN parallels myocardial ischemia, with both processes amplifying end-organ damage through hypoxic and oxidative mechanisms. In the context of DPN, confounding cardiovascular comorbidities such as hypertension and dyslipidemia are known to elevate circulating levels of NT-proBNP and cardiac troponin T (cTnT), which can complicate the specific interpretation of these biomarkers for neuropathy risk stratification.

Other Vascular Diagnostic Markers

Vascular endothelial growth factor (VEGF), endothelin-1 (ET-1), nitric oxide (NO) and endothelial nitric oxide synthase (eNOS) are associated with neuromicrovascular markers and are involved in the progression of DPN through mechanisms like endothelial dysfunction, inflammatory infiltration, and microvascular structure destruction.

VEGF (human clinical study), a key player in angiogenesis, has neuroprotective and trophic effects and is crucial for nerve repair and regeneration. However, research on VEGF levels in DPN patients has been inconsistent. A meta-analysis of 14 studies with 1983 participants (807 DPN patients, 808 non-DPN diabetes patients, and 368 healthy controls) showed significantly higher VEGF levels in DPN patients compared to non-DPN diabetes patients (SMD: 2.12 [1.34, 2.90], $P < 0.00001$) and healthy individuals (SMD: 3.50 [2.24, 4.75], $P< 0.00001$). Moreover, increased circulating VEGF levels are not linked to a higher DPN risk (OR: 1.02 [0.99, 1.05], $P < 0.00001$).[98] Recent analysis found that elevated serum VEGF - B levels are an independent DPN risk factor in T2D patients, likely related to the VEGF - B - VEGFR1 signaling pathway.[99] Cross - sectional studies also supported increased serum VEGF - B levels ($P < 0.05$).[100] VEGF negatively correlates with motor nerve amplitude and positively correlates with NSS and DNE scores. ROC analysis indicated strong diagnostic ability of VEGF (AUC: 0.807), and logistic regression identified VEGF as the only significant predictor (OR: 1.11, 95% CI (1.03, 1.20), $P= 0.0092$).[101]

ET-1 (human clinical study) functions differently from VEGF, mainly causing vasoconstriction. Some clinical trials have directly shown increased serum ET-1 levels in DPN patients.[69,102] It may act through the AGEs/ET-1/TNF - α/NOS axis in diabetes, leading to abnormal blood glucose and lipids, oxidative stress, and inflammation,[103] suggesting it could be a diabetes treatment target.[104] Recent study confirmed that ET −1 and Ang - (1–7) form a protective signal network via the physical interaction of MasR and ETBR to counteract vascular damage.[105] Decreased AMPK-eNOS

bioavailability mediates DPN development through increased apoptosis and reduced autophagy related to oxidative stress.[106] These studies offer new perspectives and research targets for DPN - induced vascular diseases.

Inflammatory Biomarkers

Emerging evidence underscores that hyperglycemia-induced oxidative stress, microvascular dysfunction, and cardiovascular comorbidities synergistically exacerbate neuroinflammatory cascades in DPN.[1,30] Cross-sectional analyses consistently identify systemic inflammation as a pivotal mediator of DPN pathogenesis, with candidate biomarkers spanning tumor necrosis factor-α (TNF-α)-associated pathways, interleukin (IL) networks, and hematologic indices like neutrophil-to-lymphocyte ratio (NLR).[107]

Meta-analyses adhering to PRISMA guidelines (15 studies) revealed markedly elevated NLR levels (human clinical study) in DPN cohorts versus diabetic controls.[93,108] Independent validation studies further established NLR's diagnostic potential, demonstrating 75% accuracy for distinguishing DPN (AUC=0.851).[109] This validate NLR as a robust inflammatory indicator. Threshold analysis demonstrated that NLR ≥2.66 significantly correlated with DPN risk (OR=1.985, 95% CI:1.29–3.05).[110] ROC curve evaluations further highlighted the superior sensitivity of combined HbA1c+NLR detection (97.2%) over individual markers (HbA1c:71.6%; NLR:90%), albeit with moderate specificity (45%) vs individual markers (HbA1c:63.8%%; NLR:50.00%).[111]

Significantly, Multicohort studies consistently report elevated systemic levels of TNF-α,[112–117] IL-6, and CRP[114] (human clinical study) are significantly increased in DPN patients. A longitudinal investigation identified baseline plasma TNF-α, IL-6, and intercellular adhesion molecule-1 (ICAM-1) as independent predictors of 5-year DPN incidence in Chinese diabetics.[118] Notably, impaired glucoregulation exacerbated TNF-α/IL-6 elevations in neuropathy subgroups compared to non-neuropathic controls.[119] US cohort data corroborated these findings, linking hs-CRP, IL-6, TNF-α, IL-1 receptor antagonist (IL-1RA), and ICAM-1 to distal sensory-motor polyneuropathy (DSPN) progression, while reduced lipocalin levels emerged as a novel risk modifier[120] (human clinical study). Electrophysiological correlations further substantiate TNF-α's pathogenic role: serum TNF-α levels inversely correlated with motor/sensory NCV (median, ulnar, peroneal, and posterior tibial nerves) in T2 DM.[121]

Overall, research on the diagnosis of DPN using inflammatory factors has made some progress, with some inflammatory factors showing good diagnostic potential.[122] For example, NLR has shown promising prospects as a clinical diagnostic biomarker for DPN, while TNF-α increases with the progression of the disease. In short-term DPN (T2DM<8 years), TNF-α levels were 43.78±26.68 pg/mL (non-neurological control group: 20.45±11.22 pg/mL; $P<0.05$); in long-term DPN (T2DM≥8 years), TNF-α levels were 74.07±32.05 pg/mL compared with the short-term group, $P<0.01$). The course of disease was positively correlated with TNF-α levels (r=0.488, $P=0.002$; r=0.478, $P=0.012$).[121] Elevated TNF-α can be used to classify the severity of neurological disorders. These accumulated evidence suggest that these inflammatory biomarkers can serve as diagnostic and clinical staging tools for DPN.

The quantitative analysis of inflammatory mediators, especially TNF-α, across DPN staging, holds promise for predictive and diagnostic applications. In order to enhance sensitivity and specificity, it is still necessary to establish large-scale longitudinal studies using multi-system inflammatory biomarkers or multi-combination biomarkers, such as oxidative stress markers (eg, MDA), cardiovascular biomarkers (eg, Hcy), and neurodamage biomarkers (eg, VEGF), in combination to establish critical values for specific stages and optimize sensitivity/specificity indicators for clinical deployment. Evaluating the clinical staging of DPN will be a good research direction.

Gene-Related Markers

Non-Coding RNA

Non-coding RNAs (ncRNAs) are a class of RNAs that are not translated into proteins.[123] Based on their functions, they can be categorized into rRNAs, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and piwi RNAs (piRNAs). ncRNAs play crucial roles in the regulation of epigenetic modifications, protein transcription, and post-transcriptional regulatory functions. In the progression of DPN, ncRNAs can influence inflammation, oxidative stress, cellular autophagy, or apoptosis processes, and may link it to clinical spheres such as other metabolic and neural

pathologies.[124] Since some ncRNAs are stably present in the blood of DPN patients, they are considered potential biomarkers that can aid in early clinical diagnosis.[123]

Using whole-transcriptome sequencing, a systematic analysis was conducted on differentially expressed mRNAs, lncRNAs, and miRNAs in the SCs of DPN rats and controls. It was found that there were 2925 mRNAs, 164 lncRNAs, and 49 miRNAs that were significantly differentially expressed in DPN rat SCs[125] (animal model, in vitro data). miRNAs and lncRNAs are two classes of genes that have been more frequently studied.

Spallone et al[126] conducted a comprehensive investigation into the expression profiles of various miRNAs in DPN and explored the underlying mechanisms from a genetic perspective. Their research revealed that miRNAs exert significant influence on oxidative stress and nerve damage by modulating multiple critical pathways, including the AGE-RAGE axis, PKC-α/NADP oxidase activity, inflammatory factors (eg, TNF-α and IL-1β), and the NF-κB signaling pathway. For instance, miR-146 (animal model) has been reduced in the sciatic nerves of diabetic mice and rats and is negatively related to inflammatory cytokines and whose mimics produce beneficial structural and functional effects.[127] In an innovative therapeutic approach, they utilized nanoparticle-miR-146a-5p (animal model) and observed notable improvements in nerve conduction velocity and reductions in demyelination. These findings underscore the potential of miRNAs as therapeutic targets for DPN. Moreover, to enhance diagnostic accuracy, they employed ROC analysis to identify various miRNAs with higher diagnostic accuracy, specificity, and sensitivity for DPN. Notably, miRNA combinations (eg, miR-128a and miR-155) (animal model) demonstrated high diagnostic efficacy (AUC>0.8) in ROC analysis, supporting their potential use as non-invasive biomarkers.

Recent studies have further elucidated the therapeutic potential of miRNAs in diabetic neuropathy through distinct molecular mechanisms. Notably, miR-503-5p (animal model) was demonstrated to mitigate neuropathic pain in T2DM murine models by targeting SEPT9 to suppress astrocyte activation,[128] while miR-186-5p exhibited significant correlations with oxidative stress markers in clinical populations.[129] Therefore, miRNAs have been considered as potential biomarkers for diabetes and its vascular complications and neuropathy,[46,130] Specific miRNAs may also be new therapeutic targets for the treatment of painful DPN.[131] The diagnostic and therapeutic potential of these regulatory molecules is amplified through their natural transport system – exosomes. These nano-vesicles facilitate intercellular communication through autocrine, paracrine, and endocrine mechanisms by shuttling ncRNAs, including functional miRNAs and mRNAs. Experimental evidence reveals their therapeutic capacity in neurological contexts: plasma-derived exosomes were shown to ameliorate peripheral neuropathy in type 1 diabetic rats via the miR-20b-3p/Stat3 axis.[132] Furthermore, comprehensive analyses have identified exosomal involvement in multiple T2DM-related pathways, with animal studies systematically evaluating their therapeutic efficacy in DPN management (see Table 3). This converging

Table 3 Role of Exosomal Components in Diabetic Neuropathy in vivo (Satyadev et al (2023))[133]

Exosomal Composition	Species	Location	Association	Potential Implication	Reference
miR-28 miR-31a miR-130a	Mouse	Serum	↑	Derived from high glucose-stimulated Schwann cells; discovery of proteins that can regulate proteins involved in neuroplasticity, axon growth, and nerve germination, which can lead to progression of neuropathic symptoms[134]	Jia et al (2018)[134]
miR-17 miR-23a miR-125b	Mouse	Serum	↓	These miRNAs are derived from MSCs and exhibit multilevel regulation of the TLR4/NF-κB and Receptor for Advanced Glycation End Product Signaling (RAGE) pathways[135]	Fan et al (2020)[135]
miR-146a	Mouse	Serum	↓	Accelerated relief of neurovascular dysfunction was observed after loading miR-146a into MSC exosomes, as measured by improved nerve conduction velocity thresholds for thermal and mechanical stimulation[136]	Fan et al (2021)[136]
miR-125a-5p	Mouse	Serum	↓	miR-125a-5p downregulates TRAF6 - mediated inflammation, providing clinical benefit through mechanical abnormalities in pain and thermal hyperalgesia measures[137]	Kasimu et al (2022)[137]

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evidence establishes a strong rationale for pursuing exosomal ncRNAs, particularly pathway-specific miRNAs, as both mechanistic biomarkers and targeted therapeutic vehicles for DPN.[133]

lncRNAs have also been shown to be involved in DPN. In a diabetic rat model, small interfering RNAs (siRNAs) targeting specific lncRNAs may attenuate DPN by decreasing the production of inflammatory factors. Using microarray analysis, 446 and 1327 differentially expressed lncRNAs were identified between diabetic patients with and without DPN.[138] The lncRNA/mRNA co-expression network in DPN patients suggests the involvement of the neurotrophic factor-MAPK signaling pathway. Several lncRNAs (CCNT2-AS1, RP1-249H1.2, CTD-3239E11.2, RP11-51B23.3, STAM-AS1, and LINC00629) have been pointed out as potential interactors in the above signaling pathway[139] (animal model).

Recent investigations have pioneered three critical advancements in diabetic peripheral neuropathy (DPN) research: (1) systematic elucidation of ncRNA regulatory mechanisms through exosome-mediated transcellular signaling (eg, miR-146a-5p nanoparticles enhancing nerve repair), (2) integration of multi-omics technologies to decode epigenetic-metabolic networks, and (3) development of nanotherapeutic strategies enabling diagnosis-to-treatment synergy. Notably, context-specific ncRNA axes (eg, miR-503-5p/SEPT9) demonstrate dual utility as mechanistic biomarkers and therapeutic targets. However, to achieve clinical translation, future studies must prioritize human tissue validation using spatial multi-omics, dynamic mapping of ncRNA interactions in neural microenvironments, and functional characterization of underexplored ncRNAs (eg, circRNAs). Addressing these gaps will bridge preclinical discoveries to precision medicine applications for DPN.

DNA Methylation (Human Clinical Study)

DNA methylation refers to the stable and reversible attachment of methyl (CH3) groups to cytosines at DNA palindromes (called CpG islands). DNA methylation is thought to be involved in regulating the expression of key genes that induce DPN. Genome-wide methylation analyses of samples collected from the same diabetic patients 16–17 years apart revealed that key genomic loci associated with diabetic complications of DNA methylation persist over time.[140] Hyperglycemia alters the DNA methylation status, thereby inducing altered gene expression associated with DPN. Significant reductions in genome-wide DNA methylation are potential biomarkers for DPN.[92,139] Genomic DNA methylation levels were significantly decreased in the DPN group compared with the non-DPN group when the duration is ≥5 years.[92] For the first time, a comprehensive analysis of peroneal nerve DNA methylation profiles in DPN patients with significant nerve regeneration and patients with significant neurodegeneration (representing two extreme DPN phenotypes) was performed. A total of 3460 differentially methylated CpG dinucleotides were identified. These differentially methylated CpG-related genes are highly enriched in biological processes related to DPN progression, such as neurodevelopment, neuronal development and axon guidance, glycerophospholipid metabolism, and mitogen-activated protein kinase (MAPK) signaling.[141]

Other Possible Genetic Diagnoses

Single locus or multigene risk is also gaining interest in the development of DPN. The development of histomics has facilitated genome-wide association studies. Studies on differentially expressed genes (DEGs) and functional enrichment analyses of DPN have also been reported.[142–144] These studies have identified co-expressed DEGs that are enriched in lipid metabolism-related pathways, signaling pathways, vascular regulation, inflammatory oxidative stress, and immunomodulatory pathways.[5,145] Many recently identified genes, including (human clinical study) the aldose reductase (AKR1B1) gene, VEGF,5,10, methylenetetrahydrofolate reductase (MTHFR) enzyme variants, APOE, and angiotensin-converting enzyme (ACE) genes, play important roles in the polyol pathway, vascular endothelial cell value-addition, and oxidative stress in endothelial cells induced by hyperhomocysteinemia. These factors are thought to be important for the pathogenesis of diabetic neuropathy.[19] Vitamin B12, an essential cofactor for the degradation of methylmalonic acid and the synthesis of methionine from homocysteine, exerts intrinsic antioxidant properties both in vivo and in vitro. The presence of oxidative stress in vitamin B12-deficient patients suggests that the neurological changes observed in patients with DPN may be caused by cellular B12 deficiency.[146] Emerging evidence suggests PARP-1-targeted siRNA (animal model) therapy attenuates diabetic peripheral neuropathy in streptozotocin-induced rats by coordinately modulating

oxidative-inflammatory-apoptotic axes. This intervention significantly reduces oxidative stress (MDA, $P < 0.001$) while restoring antioxidant defenses (GSH, CAT, SOD, $P < 0.001$), and concurrently suppresses pro-inflammatory mediators (NF-κB, IL-6, IL-1β, TNF-α, TGF-β) and apoptotic executors (Caspase-3/9, Bak, Bax) with statistical significance ($P < 0.01$).[147]

All of these target genes may be candidate biomarkers for DPN. Other possible genes will not be further excavated here. However, regardless of the type of genes, there is still a lack of in-depth studies with large sample data.

Metabolic Diagnostic Markers (Human Clinical Study)

Metabolic dysregulation is increasingly recognized as a critical contributor to the progression of DPN. Comprehensive profiling of diabetes-associated metabolites in biological matrices using analytical chemistry techniques has revealed potential biomarkers for early DPN diagnosis, including amino acids, organic acids, fatty acids, lipids, and carbohydrates.

Comparative studies demonstrate distinct lipid profile alterations in T2DM patients with DPN. Serum triglycerides and alanine aminotransferase levels are significantly elevated, whereas C-peptide and total cholesterol levels are reduced compared to non-neuropathic controls.[148] Hypertriglyceridemia is independently associated with both the loss of myelinated peroneal nerve fiber density[144] and an increased risk of lower limb amputation in T2DM.[143] Although reduced HDL-cholesterol has been implicated as a DPN risk factor in some studies,[149] meta-analytic evidence indicates this association is significant only in T1DM-related neuropathy ($P<0.05$), with no statistically significant difference observed in T2DM cohorts.[150] Beyond lipid metabolism, A ^{1}H-NMR metabolomics study revealed significantly reduced serum formate levels in DPN patients versus T2DM controls ($P<0.001$, AUC=0.981), showing negative correlations with HbA1c, uric acid (UA), and cystatin C ($P<0.05$), and positive association with albumin. These findings position formate as a biomarker implicating mitochondrial dysfunction and gut dysbiosis in DPN pathogenesis, with dual diagnostic and therapeutic potential.[151] Additionally, Pre-analytical variables such as fasting status, sample processing time, and storage conditions can critically influence the stability and measured concentrations of metabolites, potentially introducing significant bias into biomarker studies for DPN.

Liquid chromatography-based metabolomic analysis of T2DM patients with distal symmetrical sensorimotor polyneuropathy (DSPN) identified 16 plasma metabolites and 3 cholesterol derivatives as discriminative markers. Among these (human clinical study), phenylalanine, alanine, lysine, tryptophan, and SMC16:0 exhibited the highest diagnostic potential for distinguishing DSPN from non-DSPN cases ($P<0.05$).[152]

Challenge and Discussion

DPN is diagnosed based on clinical symptoms and ancillary tests such as electrophysiological studies. Per the Expert Consensus on Diabetic Neuropathy (2021), diagnostic criteria require: Confirmed diabetes history; Neuropathy onset post-diabetes diagnosis; Neuropathic symptoms (eg, pain, numbness) plus ≥1 abnormal neurological test (eg, impaired ankle reflex, sensory perception); Asymptomatic cases require ≥2 abnormal test results.[31]

The clinical diagnosis of DPN currently relies on electrophysiological methods, which are operationally complex, cost-intensive, and prone to diagnostic inaccuracies. While existing diagnostic approaches and biomarkers show potential, their clinical utility is limited by inconsistent methodologies, lack of standardized diagnostic staging criteria, and susceptibility to confounding variables. For instance, oxidative stress markers such as MDA[69,71] exhibit population-specific variability and may present aberrant levels in non-diabetic neuropathies, undermining their diagnostic specificity. Similarly, NSE, though indicative of neural injury, demonstrates limited specificity due to elevations in diverse neurological disorders and malignancies.[153,154] The absence of harmonized detection protocols and validated diagnostic thresholds further complicates cross-study comparability. Critically, single-marker analyses fail to capture the multifactorial progression of DPN, as exemplified by TNF-α, which reflects inflammatory processes but provides no insight into concurrent neurovascular or metabolic dysfunction.

A multimodal approach integrating functional, structural, and molecular biomarkers could enhance diagnostic precision. Combining nerve conduction studies (eg, NCV, F-wave parameters) with neural injury markers (eg, NF-H, MPZ) enables simultaneous assessment of functional impairment and structural degeneration. Similarly, pairing oxidative stress markers (MDA, GSH) with inflammatory indices (NLR, TNF-α) may provide a holistic evaluation of disease

mechanisms. Machine learning approaches offer powerful tools for integrating multimodal data in DPN biomarker discovery, with convolutional neural networks (CNNs) and random forests (RFs) representing two distinct paradigms. CNNs excel at analyzing high-dimensional, spatially structured data like corneal confocal microscopy images or nerve ultrasound, automatically extracting complex hierarchical features for superior pattern recognition. In contrast, RFs are particularly effective for processing structured, tabular data—such as combining clinical scores, biochemical parameters, and quantitative sensory thresholds—by identifying non-linear interactions and providing interpretable feature importance rankings. While CNNs achieve high accuracy in image-based diagnostics, their "black-box" nature contrasts with the inherent explainability of RFs, which can reveal key predictive biomarkers from heterogeneous clinical datasets. Current evidence highlights promising candidates such as Hcy, NLR, and TNF-α for monitoring DPN progression, while oxidative stress markers and genetic biomarkers require further validation of their diagnostic thresholds and specificity.

As illustrated in Table 4, we have integrated the potential biomarkers for Diabetic Peripheral Neuropathy (DPN). This integration underscores a pivotal conceptual advancement: DPN is not the result of a single pathway disruption. Instead, it emerges from a complex "pathological network" formed by the dynamic interaction of multiple systems, including oxidative stress, inflammation, and neurovascular injury.

Translation of these biomarkers into clinical practice necessitates three critical steps: establishing large-scale, multi-ethnic cohort studies to elucidate the molecular pathways of biomarker neuropathy associations, establishing population specific diagnostic thresholds through ROC curve analysis using standardized multicenter trials, and conducting comparative studies in different genetic backgrounds (eg Asian and Caucasian cohorts) to address potential biomarker sensitivity variability (Δ>15% in pilot studies) and specificity. Current evidence suggests that to achieve a clinical application sensitivity/specificity of ≥80%, validation is required in cohorts of over 5000 participants from more than 3 races, supplemented by longitudinal data on biomarker stability and disease progression correlation ($r > 6$).

Emerging technologies, particularly artificial intelligence (eg, CNN-LSTM deep learning architectures), could accelerate biomarker discovery by enabling multimodal data integration and early detection of subclinical abnormalities during the impaired glucose tolerance phase. This review systematically categorizes biomarkers by pathogenic mechanism (neural conduction deficits, oxidative stress, inflammation, neurovascular injury, metabolic dysregulation, and genetic factors) to provide clinicians with a framework for interpreting complex DPN pathophysiology (Figure 5). We fully acknowledge the inherent heterogeneity among studies, whether clinical, animal, or cellular. It is undeniable that direct, point-by-point comparisons of outcomes across all cited studies are impractical due to significant variations in

Table 4 An Integrated View: Crosstalk Among Oxidative Stress, Inflammation, and Neurovascular Dysfunction

Interaction Category	Specific Examples & Potential Mechanisms	Examples of Associated Biomarkers	Relevant Research Methods & Implications
Oxidative Stress Driving Inflammation	Reactive Oxygen Species (ROS) act as signaling molecules that activate inflammatory pathways such as NF-κB, promoting the expression of inflammatory factors like TNF-α and IL-6.	MDA/8-OHdG (oxidative damage products) → IL-6/ TNF-α (inflammatory factors)	Explain how "metabolic memory" may cause sustained activation of this pathway through epigenetic modifications.
Inflammation Exacerbating Oxidative Stress & Vascular Injury	Inflammatory cell infiltration releases more ROS; inflammatory factors impair endothelial function and disrupt the blood-nerve barrier.	CRP/IL-1β (inflammation) → Endocan (endothelial injury)	Cite neuroimmunology studies to illustrate the interaction between peripheral inflammation and the central nervous system.
Vicious Cycle of Vascular Injury and Ischemic Hypoxia	Endoneurial microvascularopathy leads to hypoxia, inducing Hypoxia-Inducible Factor (HIF-1α), which subsequently upregulates VEGF and aggravates oxidative stress.	Microvascular flow abnormalities → HIF-1α/ VEGF → Oxidative stress products	Link to ischemic changes found in neuroelectrophysiological tests.
Common Upstream Regulatory Nodes	Receptors such as TLR4 can be activated by both oxidation-modified products (eg, oxidized lipids) and endogenous damage-associated molecular patterns, downstream linking oxidative and inflammatory responses.	TLR4 → MyD88/NF-κB (inflammation) and NADPH oxidase (oxidative)	Highlight the potential of hub molecules like TLR4 as targets for multi-target therapeutic intervention.

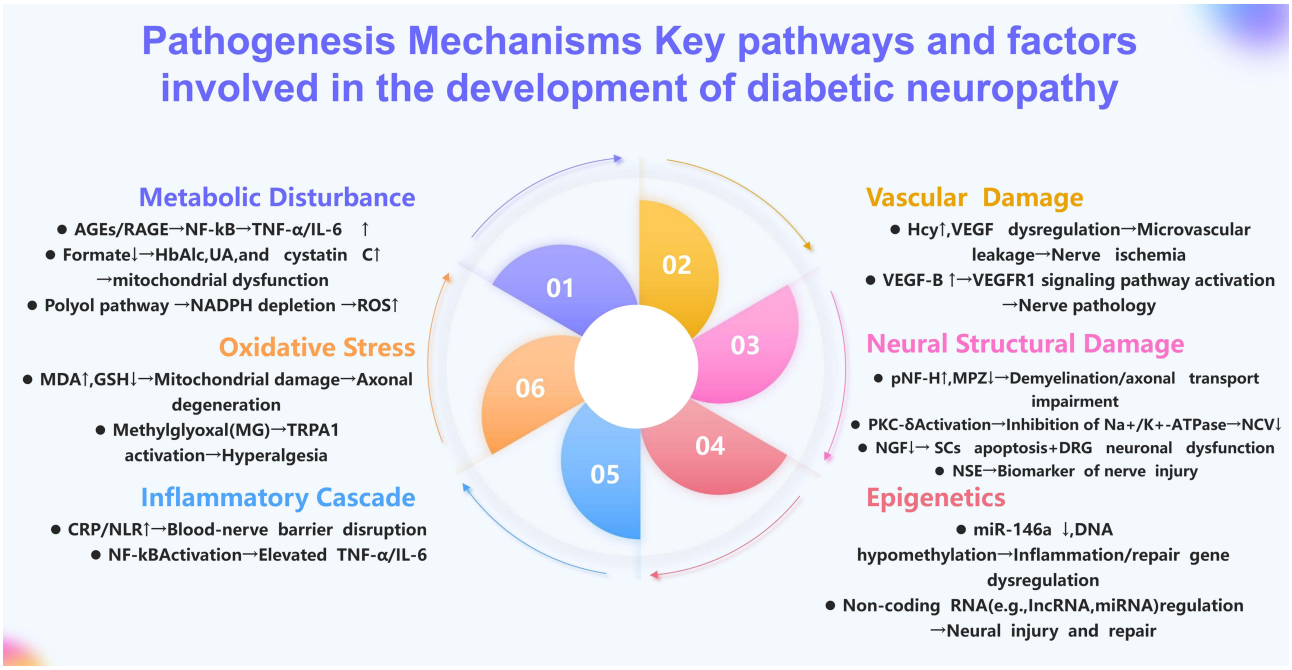

Figure 5 Pathogenesis Mechanisms Key pathways and factors involved in the development of diabetic neuropathy.

study design, population characteristics, and experimental models, which inevitably influence the reported parameters. Nevertheless, the biomarkers discussed in this article provide valuable reference points for guiding more targeted future research. This is particularly true for findings that demonstrate consistency across different research models. For instance, the specific alterations in markers of oxidative stress, neurovascular injury, and certain inflammatory pathways have been robustly observed in both animal models of DPN and in human patients. These convergent points across species should garner focused attention from researchers, as they may illuminate the most promising pathways for future clinical translation.

Future diagnostic strategies should prioritize the development and validation of multimodal biomarker panels that integrate complementary pathophysiological information from metabolic, inflammatory, and neurotrophic pathways, as such panels are expected to outperform single biomarkers in sensitivity, specificity, and their ability to guide personalized therapeutic interventions for DPN. While current biomarkers remain preclinical, their clinical adoption requires rigorous validation across diverse populations and standardized implementation. Only through such efforts can we achieve the target diagnostic ensitivity/specificity of ≥80% essential for cost-effective, stage-specific DPN management.

Conclusion

Current research on DPN biomarkers encompasses a diverse array of candidates, including oxidative stress mediators, neural injury proteins, inflammatory cytokines, vascular dysfunction markers, metabolic intermediates, and genetic/epigenetic regulators; however, their clinical translation remains constrained by a predominant reliance on cross-sectional studies, lack of standardized diagnostic thresholds, and insufficient validation in large, multi-ethnic prospective cohorts.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

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Qingqin Lyu, Yanyan Tan and Xianqi Zeng contributed equally to this paper and should be considered co-first authors.

Author Contributions

ML: Writing–original draft, Writing–review and editing, Conceptualization, Data curation, Funding acquisition, Investigation, Methodology. QL, YT, XZ: Data curation, Formal analysis, Methodology, Writing–original draft. SP: Conceptualization, Investigation, Project administration, Supervision, Writing–review and editing. All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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