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# Diabetic Peripheral Neuropathy – From Early Symptoms to Long-Term Complications and Treatment Strategies

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## Abstract

**Introduction**: Diabetic peripheral neuropathy (DPN) is a common and clinically important complication of diabetes, associated with sensory dysfunction, neuropathic pain, gait impairment, diabetic foot ulceration, amputation risk, and reduced quality of life. Early stages may be asymptomatic or difficult to recognize.

**Aim of the study**: This narrative review aimed to synthesize current knowledge on DPN, including early symptoms, pathophysiology, diagnosis, long-term complications, treatment, prevention of progression, and future perspectives.

**Materials and methods**: This article was prepared as a narrative review, not a systematic review or meta-analysis. Relevant literature was identified through PubMed and Google Scholar. Peer-reviewed articles, reviews, meta-analyses, clinical guidelines, and original studies on DPN were selected according to clinical relevance and contribution to the topic.

**Results**: DPN is a multifactorial, progressive, length-dependent sensorimotor polyneuropathy involving metabolic, vascular, inflammatory, oxidative, mitochondrial, and neuronal-glial mechanisms. Hyperglycemia, dyslipidemia, obesity, insulin resistance, microvascular injury, and genetic susceptibility may contribute to small- and large-fiber damage. Clinical manifestations include burning, tingling, electric shock-like pain, numbness, sensory loss, impaired protective sensation, gait instability, foot deformity, ulceration, amputation risk, sleep disturbance, emotional burden, and reduced daily functioning. Management includes glycemic and metabolic risk-factor control, screening, foot protection, pharmacological and topical pain treatment, rehabilitation, lifestyle modification, patient education, and selected emerging or pathogenetically oriented therapies. However, current treatments mainly relieve symptoms and do not reliably reverse established nerve damage.

**Conclusions**: DPN requires early recognition, individualized assessment, realistic treatment goals, and multidisciplinary care focused on pain reduction, foot safety, mobility, daily functioning, and quality of life. Further research is needed to validate biomarkers, improve risk stratification, and develop effective disease-modifying therapies.

**Keywords:** diabetic peripheral neuropathy, diabetic neuropathy, neuropathic pain, early diagnosis, diabetic foot, glycemic control, treatment strategies, quality of life

## 1. Introduction

Diabetic peripheral neuropathy (DPN) is a common and clinically consequential complication of diabetes, affecting up to about half of people with diabetes in some populations and being associated with sensory loss, gait dysfunction, foot ulceration, and lower-limb amputation [33]. Its burden extends beyond neuropathic pain, as sensory and motor dysfunction can impair daily activities and independence, while chronic pain may disturb sleep and limit social or occupational participation. Early DPN may be insidious or asymptomatic, and current treatment largely focuses on glycemic control and symptom management rather than reversal of nerve damage, which contributes to the continuing clinical and health-system burden of the disease [28].

In its typical form, DPN is represented by diabetic sensorimotor peripheral neuropathy, the most prevalent diabetic neuropathic syndrome, defined as a symmetrical, length-dependent sensorimotor polyneuropathy. It usually begins in the toes, progresses to the feet and legs in a stocking distribution, and may involve the upper limbs once lower-limb disease is established. Early manifestations may include numbness, paraesthesia, and neuropathic pain described as burning, sharp, cold, aching, or electric-shock-like; examination may also reveal length-dependent impairment of pain, temperature, vibration, light touch, or proprioception. As sensory deficits accumulate, loss of protective sensation becomes particularly important because it is a major risk factor for diabetic foot ulceration, while advanced neuropathy may contribute to sensory ataxia, foot deformity, muscle weakness, and falls [1].

Because DPN progresses gradually with diabetes duration and is linked to metabolic and microvascular alterations, it cannot be understood through a single clinical lens. The condition involves mechanisms of nerve injury, risk factors, early sensory manifestations, screening and diagnostic challenges, pain treatment, prevention of complications, and the search for disease-modifying approaches [7]. A narrative structure can therefore follow the clinical pathway from early symptoms and clinical suspicion to examination, diagnosis, monitoring, treatment, and prevention. By integrating risk factors, clinical forms, screening methods, and current therapeutic options, this approach presents DPN as a progressive clinical problem rather than a set of isolated findings [23].

Despite an expanding evidence base, DPN often remains difficult to recognize early because nerve-fiber injury may precede the full clinical picture, and the condition is still underdiagnosed in many patients. Some patients report burning, tingling, or electric-shock-like pain, whereas others develop numbness, poor balance, unsteadiness, or loss of protective sensation and may first present after falls or foot complications such as ulcers [2]. This variability creates a practical challenge for routine care, which requires regular screening, targeted history-taking, sensory and reflex testing, risk-factor management, foot-ulcer risk evaluation, and individualized pain-focused treatment. In painful DPN, treatment aims to reduce pain and improve functioning, sleep, mood, and quality of life; however, complete pain resolution is rare, and disease-modifying interventions that reliably prevent or reverse nerve damage remain an important research priority [36]. Accordingly, this review approaches DPN as a clinical continuum, moving from early symptoms and mechanisms to diagnosis, complications, treatment strategies, and prevention.

## 2. Methodology of the Narrative Review

This narrative review presents diabetic peripheral neuropathy (DPN) as a continuum from early sensory symptoms and pathophysiological mechanisms to diagnosis, long-term complications, treatment, prevention of progression, and future perspectives. It was not designed as a systematic review or meta-analysis; therefore, no formal PRISMA-based selection process, protocol registration, quantitative synthesis, or standardized risk-of-bias assessment was performed. The aim was to integrate current clinical and biological knowledge into a coherent discussion relevant to patient care.

Relevant literature was identified through PubMed and Google Scholar searches, last updated on 24 June 2026. Search terms included “diabetic peripheral neuropathy” with terms related to early symptoms, pathophysiology, risk factors, diagnosis, screening, neuropathic pain, diabetic foot complications, treatment strategies, prevention of progression, biomarkers, small-fiber neuropathy, and future perspectives. AND/OR operators were used where appropriate. Google Scholar results were assessed for consistency with the review scope, and reference lists of selected publications were checked for additional sources.

The review considered peer-reviewed articles, clinical guidelines, systematic reviews, meta-analyses, narrative reviews, and original studies relevant to DPN. Priority was given to sources addressing epidemiology, disease burden, nerve-injury mechanisms, risk factors, diagnosis and screening, neuropathic pain, diabetic foot complications, rehabilitation, treatment, prevention, biomarkers, and emerging therapies. Publications were excluded if they were unrelated to DPN, focused mainly on other neuropathies or conditions, were not peer reviewed, or had limited clinical or mechanistic value.

Sources were selected according to clinical relevance, scientific quality, recency, and contribution to the manuscript's thematic structure. Because this was a narrative review, studies were interpreted within the overall clinical synthesis rather than graded with a formal evidence-assessment tool. The included literature was organized thematically to follow the DPN clinical pathway, linking mechanisms and risk factors with symptoms, diagnosis, complications, treatment, prevention, and future perspectives.

Limitations include possible selective literature inclusion and lower reproducibility and formal evidence ranking than systematic reviews. No quantitative comparison of study populations, diagnostic criteria, or treatment outcomes was performed. Emerging areas, including biomarkers, digital tools, microbiota-related interventions, and mechanism-oriented therapies, remain under investigation and require further validation before routine clinical use.

## 3. Pathophysiology and Risk Factors of Diabetic Peripheral Neuropathy

### 3.1. Metabolic and Bioenergetic Mechanisms of Nerve Injury

Understanding why DPN usually appears first in the feet requires attention not only to hyperglycemia, but also to the length-dependent anatomy and high energy demands of peripheral nerves. The longest axons, particularly those supplying the lower limbs, depend on adequate energy distribution, Schwann-cell support, vascular integrity, and glia–axon communication. In this setting, metabolic and bioenergetic failure is linked to distal-to-proximal nerve damage, helping to explain why burning pain, altered temperature perception, or numbness usually begin distally [34]. DPN is therefore better described as a multifactorial process involving metabolic dysregulation, mitochondrial impairment, oxidative stress, inflammation, neurovascular injury, and neuronal–glial damage, rather than as a single glucose-driven pathway. This perspective links early sensory symptoms with progressive nerve-fiber injury, diabetic foot ulceration, and amputation risk [5].

Within this framework, chronic hyperglycemia represents a sustained metabolic burden on peripheral nerves. Under high-glucose conditions, excess glucose is redirected into the polyol and hexosamine pathways and is linked to AGE formation, PKC activation, oxidative stress, and mitochondrial dysfunction [19]. Although these mechanisms are often discussed separately, they appear to converge on impaired Schwann-cell support, endothelial injury, mitochondrial dysfunction, oxidative stress, and progressive nerve damage. Clinically, this helps explain why injury may develop before advanced sensory loss or late foot complications become evident. Hyperglycemia should therefore be regarded as a critically important contributor to DPN, but not as an isolated cause; it acts within a broader network of metabolic, vascular, inflammatory, and glial disturbances [33].

The metabolic background of DPN extends beyond hyperglycemia, particularly in type 2 diabetes, where obesity, insulin resistance, dyslipidemia, and other metabolic-syndrome components may increase neuropathy risk [34]. Obesity and type 2 diabetes are often accompanied by elevated triglycerides, increased free fatty acids, altered lipoprotein profiles, and qualitative lipid changes. Observational studies have linked adverse lipid profiles with DPN prevalence or severity, even after adjustment for glycemic indices. Lipid dysregulation is thought to contribute through mitochondrial dysfunction, impaired β-oxidation and ATP production, oxidative stress, neuroinflammation, endothelial dysfunction, reduced microcirculation, and peripheral nerve damage. These findings support viewing dyslipidemia as a potential pathogenic contributor rather than a simple laboratory abnormality. Lipidomic studies have reported changes in acylcarnitines, sphingolipids, phospholipids, triglyceride metabolism, and free fatty acids, but profiling remains heterogeneous and is not yet ready for routine clinical use [14].

### 3.2. Inflammation, Microvascular Dysfunction, and Neurovascular Damage

In this metabolic environment, inflammation should be understood as part of a broader pathogenic network rather than as an isolated cause of DPN. Experimental evidence suggests that diabetes, obesity, and dyslipidemia may be accompanied by low-grade intraneural inflammation, including macrophage and T-cell infiltration, increased soluble cytokines in the sciatic nerve, and degeneration of intraepidermal small nerve fibers [18]. This activity appears to intersect with hyperglycemia-, dyslipidemia-, and insulin-resistance–related oxidative stress and mitochondrial dysfunction, potentially favoring progressive nerve damage. Proinflammatory cytokines, chemokines, adhesion molecules, Schwann-cell and glial signaling, and macrophage polarization have all been implicated in DPN, with several inflammatory markers linked to nerve injury, neuropathic pain, or sensory dysfunction. Clinically, immune activation may help connect early small-fiber injury, progressive sensory abnormalities, and painful DPN [17].

Peripheral sensory nerves depend on local microvascular delivery of oxygen and nutrients, particularly in the diabetic metabolic environment. In DPN, metabolic disturbances are accompanied by hyperglycemia-related vascular injury, reduced blood supply, capillary basement membrane thickening, endothelial changes, and hypoxia, all of which may contribute to distal nerve-fiber damage and altered sensory perception. This does not imply that ischemia alone explains DPN; vascular dysfunction is better viewed as one component of a broader metabolic, oxidative, and inflammatory injury pattern [24]. Pathological and experimental studies also suggest that M1 macrophage infiltration can evoke oxidative stress, disturb retrograde axonal transport, and be associated with DRG neuronal atrophy. Together, these vascular and inflammatory changes may undermine the microenvironment needed to preserve axonal integrity, conduction, and sensory function [30].

### 3.3. Genetic Susceptibility and Clinical Heterogeneity

Even after metabolic, lipid-related, inflammatory, and vascular mechanisms are considered, DPN remains a heterogeneous condition. Some patients develop neuropathic complications early, even at the stage of prediabetes, whereas others show little evidence of neuropathy despite long-standing diabetes, suggesting that glycemia and disease duration do not fully explain individual susceptibility. Genetic studies have identified candidate variants and pathways related to oxidative stress, inflammatory and defense responses, glucose and lipid metabolism, vascular regulation, axonogenesis, and neurotrophic signaling, which may contribute to DPN susceptibility and, in some cases, progression [26]. This variability is consistent with the clinical spectrum of DPN, ranging from burning pain to numbness, reduced sensation, or mixed small- and large-fiber involvement. Emerging models that integrate genetic, epigenetic, metabolic, and phenotypic information may support risk stratification and precision medicine, but prospective validation and reliable biomarkers are still needed before routine use [29].

### 3.4. Clinical Risk Profile and Lifestyle-Related Influences

In clinical practice, established risk factors remain essential for identifying patients who may require closer screening. DPN risk is higher with longer diabetes duration, older age, poorer glycemic control or higher HbA1c, hypertension, dyslipidemia, obesity, smoking, and coexisting microvascular complications such as retinopathy or nephropathy. Because these factors differ in strength and clinical context, they are best interpreted as a risk profile that supports timely screening, foot examination, and preventive counseling rather than as an equal-weight checklist [6]. Painful DPN adds further complexity, as its reported risk pattern partly overlaps with general DPN while also emphasizing female sex, HbA1c, nephropathy, retinopathy, cardiovascular disease, arterial hypertension, obesity, smoking, age at onset, and diabetes duration. Risk assessment is therefore practical as well as predictive, guiding earlier screening and interventions aimed at reducing complications and quality-of-life burden [13].

DPN should also be considered in relation to modifiable lifestyle factors, particularly dietary patterns and physical activity. Diet may affect DPN-relevant mechanisms such as insulin resistance, dyslipidemia, oxidative stress, chronic inflammation, and microvascular dysfunction, while research on gut microbiota and the gut–nerve axis remains promising but still developing. Diet or microbiota-targeted strategies should therefore be presented as modifiable influences within broader prevention and management, not as proven stand-alone treatments capable of reversing established neuropathy [27]. Physical activity should likewise be framed as clinically useful but individualized. Exercise may reduce hyperglycemia-related stress and improve mobility, balance, gait, neuropathic symptoms, pain, and quality of life, while prescription in DPN should consider cardiovascular clearance, hypoglycemia, orthostasis, glucose monitoring, and musculoskeletal or skin-related injury risk. Together, these lifestyle factors provide a practical bridge between pathophysiological risk, prevention, and symptom-oriented management [2].

## 4. Early Symptoms and Clinical Presentation

### 4.1. Small-Fiber Involvement and Early Sensory Symptoms

Early DPN may first involve small Aδ and C fibers, which transmit pain and temperature information and contribute to autonomic regulation. Their degeneration may remain largely subclinical, precede large-fiber damage, and, through sudomotor dysfunction, later be associated with dry skin, reduced sweating, or skin cracks [16]. These features should be interpreted cautiously rather than dismissed, because conventional nerve conduction studies do not detect small-fiber pathology, whereas emerging neurophysiological biomarkers may help identify small-fiber and early large-fiber damage [11].

When small-fiber involvement becomes clinically apparent, early DPN is usually recognized through distal sensory complaints, particularly in the feet. Recent-onset foot pain described as tingling, burning, or prickling has been linked with early C- and Aδ-fiber damage, and DPN is characterized by distal-to-proximal axonal loss. Common symptoms include symmetrical distal limb pain, tingling, numbness, and pain described as burning, electric, sharp, or dull aching, often worsening at night, with tiredness, or during stress [22]. Because DPN phenotypes may be painful, painless, or mixed, and may differ in pain intensity, sleep disturbance, sensory profile, and quality-of-life impact, early assessment should focus on the patient's individual symptom pattern and functional burden rather than on a fixed checklist [12].

### 4.2. Painful Diabetic Peripheral Neuropathy

For a clinically important subgroup of patients, DPN is experienced primarily through painful neuropathic symptoms rather than numbness alone. Painful DPN affects approximately 20–24% of people with diabetes and is characterized by burning, tingling, and electric shock-like sensations, which may coexist with numbness, paraesthesia, allodynia, or hyperalgesia. It is associated with impaired daily functioning, depression, sleep disturbance, financial instability, reduced quality of life, and pain that may be worsened by poor sleep and low mood [36]. In small-fiber DPN, pain may also be described as lancinating, shooting, or stabbing, and is typically worse at night [2].

### 4.3. Painless Neuropathy and Loss of Protective Sensation

Unlike painful DPN, painless presentations may be clinically deceptive because sensory loss can progress without pain. Some patients develop a predominantly painless phenotype with numbness, tingling, loss of sensation, and reduced perception of light touch, vibration, or temperature [12]. In daily life, loss of protective sensation may allow high-pressure areas, blisters, or minor injuries to go unnoticed, especially when footwear is poorly fitted or the feet are not inspected regularly. Preventive foot care should therefore include daily inspection for injuries, blisters, or infection, appropriate footwear, and regular foot examinations to support early detection and management of foot problems [6].

### 4.4. Atypical Presentations and Differential Clinical Patterns

Although distal symmetrical sensorimotor polyneuropathy is the most prevalent neuropathic syndrome in diabetes, diabetic neuropathies include a heterogeneous group of clinical syndromes. Autonomic neuropathy may affect cardiovascular, gastrointestinal, urogenital, sudomotor, metabolic, or pupillary functions, whereas focal and multifocal neuropathies may present as mononeuropathies, entrapment neuropathies, or radiculoplexus syndromes with different timing and anatomical distribution [1]. This distinction is clinically important because asymmetry, rapid or subacute onset, cranial nerve involvement, proximal pain with weakness, or an atypical anatomical pattern should prompt consideration of focal, multifocal, treatment-induced, compressive, microvasculitic, or other non-diabetic causes rather than being assumed to represent classical DSPN. Diagnosis should therefore rely on careful clinical assessment, appropriate screening, and exclusion of alternative causes [23].

## 5. Diagnosis and Screening

### 5.1. Screening Recommendations and Clinical Assessment

Once DPN is clinically considered, assessment should focus on active detection rather than waiting for advanced foot complications. ADA-referenced guidance recommends screening at diagnosis in type 2 diabetes and five years after the onset of type 1 diabetes, which is important because approximately half of patients with diabetic neuropathy may be asymptomatic [23]. Reduced pain or protective sensation may allow minor lower-limb trauma to go unnoticed, increasing the risk of foot ulceration. Regular assessment can identify patients requiring closer foot-focused follow-up and help distinguish typical DPN from atypical presentations that require neurological work-up, making otherwise unrecognized neuropathic risk clinically visible and actionable [7].

When screening raises the possibility of DPN, diagnosis should begin with a targeted history that addresses both positive sensory symptoms and sensory loss. The history should explore a distal, symmetrical, often distal-to-proximal pattern and symptoms such as numbness, tingling, burning, stabbing or shooting pain, altered thermal sensation, allodynia, poor balance, gait difficulty, and interference with daily activities. These findings should be paired with a focused neurological examination of small- and large-fiber function, including pinprick or temperature sensation, light touch, vibration, proprioception, ankle reflexes, balance or gait, and careful foot inspection [7]. This combined approach is important because DPN may be painful, painless, or initially asymptomatic, and clinically relevant disease may appear as reported discomfort, reduced sensation, impaired reflexes, loss of protective sensation, or ulcer risk detected during examination [2].

### 5.2. Bedside Diagnostic Tools and Foot-Risk Evaluation

After history and neurological examination, bedside tests can document sensory loss and estimate foot-ulcer risk in suspected DPN. Common tools include the 10-g monofilament, 128-Hz tuning fork, Ipswich Touch Test, and VibraTip; however, they are not interchangeable. Monofilament and vibration-based assessments mainly evaluate protective sensation or large-fiber dysfunction, whereas Neuropad and Sudoscan assess sudomotor or small-fiber-related abnormalities and may support earlier detection in selected settings [4]. These tests support, rather than replace, clinical judgment by helping clinicians identify patients who require closer foot-risk assessment, education, referral to foot-protection services, or further evaluation before sensory loss contributes to ulceration or other preventable complications [3].

### 5.3. Clinical Scores, Quantitative Sensory Testing, and Electrophysiology

When bedside screening suggests neuropathy, assessment should move beyond a simple yes-or-no impression toward a structured description of DPN presence, severity, and clinical presentation. Composite tools such as the MNSI, NDS, and Toronto-based clinical neuropathy scores have been developed and validated to support more consistent assessment, although they are best interpreted as supportive tools rather than highly sensitive stand-alone measures of subtle progression [10]. A score should not replace the patient's clinical story, because patients may differ in pain burden, sleep disturbance, balance or gait impairment, and functional impact. Quantitative sensory testing can add phenotypic detail by measuring responses to controlled thermal, vibration, mechanical, and pressure stimuli, helping characterize sensory signs in painful, painless, and mixed forms of DPN [12].

When bedside assessment remains ambiguous, targeted electrophysiological or small-fiber testing may help document the pattern of nerve involvement. Nerve conduction studies are established biomarkers of large-fiber neuropathy, providing diagnostic and staging information and documenting axonal loss or demyelinating features, but they do not directly assess thinly myelinated Aδ or unmyelinated C fibers. In selected cases, skin biopsy with IENFD assessment, corneal confocal microscopy, and laser-evoked potentials can add structural or functional information about small-fiber involvement [11]. This limitation is clinically relevant because small-fiber involvement may be associated with pain, altered thermal sensation, or autonomic features even when nerve conduction studies do not yet show objective large-fiber involvement. Sudomotor tests such as Neuropad or Sudoscan may provide additional information when autonomic or sweat-related small-fiber dysfunction is suspected, but they are best reserved for selected, ambiguous, or specialist contexts rather than treated as routine requirements for every typical DPN presentation [16].

### 5.4. Differential Diagnosis and Atypical Features

A careful diagnostic pathway should remind clinicians that neuropathic symptoms in a person with diabetes are not automatically attributable to typical DPN. A length-dependent, stocking-glove pattern beginning in the toes and ascending the legs is consistent with typical DPN, whereas acute or subacute onset, non–length-dependent findings, motor predominance, or asymmetry should prompt consideration of alternative diagnoses and other peripheral nervous system conditions [33]. In such cases, the task is not to reject DPN automatically, but to assess whether another potentially treatable neuropathy is mimicking or coexisting with it. Potential contributors include vitamin B12 deficiency, alcohol or toxic exposure, thyroid or renal disease, nutritional deficiencies, chronic inflammatory demyelinating polyradiculoneuropathy, hereditary or genetic neuropathies, and systemic disorders such as vasculitis, paraproteinemia, or amyloidosis. Accurate attribution is clinically important because selected mimics or coexisting neuropathies may require laboratory testing, neurological referral, or different treatment [2].

## 6. Long-Term Complications

### 6.1. Diabetic Foot Ulceration and Amputation Risk

Screening is intended to identify DPN-related foot risk before minor, often painless injuries progress to ulceration or amputation. When DPN reduces protective sensation, high-pressure areas, blisters, or small injuries may go unnoticed, making daily inspection, appropriate footwear, regular foot examinations, and patient education central to prevention [6]. Over time, these lesions may be compounded by abnormal foot loading, deformity, dry skin, infection, peripheral vascular disease, delayed diagnosis, poor wound healing, or inadequate management. Progression from ulceration to amputation should therefore be presented not as inevitable, but as a potentially preventable pathway in which neuropathy, vascular risk, missed injury, and delayed or insufficient care may converge [1].

### 6.2. Gait Instability, Falls, and Mobility Impairment

Beyond ulceration and amputation, DPN can make walking less stable and more cognitively demanding. As proprioceptive and tactile feedback from the lower limbs becomes less reliable, gait is often more conservative, with slower speed, shorter steps, longer double-support time, and, in some studies, greater step width. Visual and vestibular input, muscle weakness, pain, cognitive demands, and impaired neuromuscular control may further contribute to postural and gait instability [25]. These changes should be understood as risk factors rather than a fixed trajectory toward falls. They are clinically important because swelling, trauma, or fracture may be less obvious in a neuropathic foot, and fracture should be considered even in the absence of pain or a clear trauma history [32].

### 6.3. Pain, Sleep Disturbance, and Emotional Burden

Painful DPN can create a substantial long-term burden, particularly when pain worsens at night and disrupts sleep. Symptoms may include burning, tingling, stabbing or electric shock-like pain, allodynia, hyperesthesia, altered thermal sensations, or other distal discomfort. However, pain should not be presented as universal, because only a subset of patients develops painful DPN. When present, pain intensity is consistently associated with poorer sleep quality, lower quality of life, depression, anxiety, sleep deprivation, impaired functioning, and reduced work productivity. Pain may also coexist with sensory loss, gait abnormalities, and postural instability in mixed phenotypes [12]. This is clinically relevant because DPN-related loss of proprioception, cutaneous sensation, and lower-limb reflex input can delay balance-correcting responses and increase fall-related injury risk; therefore, a painful foot should not be assumed to be safe or well protected [15].

### 6.4. Impact on Daily Functioning and Quality of Life

DPN should be understood as a complication that affects daily functioning and quality of life, not only neurological sensation. In some patients, numbness, neuropathic pain, unsteadiness, and loss of protective sensation may influence walking, footwear choices, and the need for daily foot inspection, especially when advanced neuropathy combines sensory ataxia, foot deformity, muscle weakness, fall risk, and ulcer risk [1]. The burden varies between patients, since neuropathic pain is common but not universal; however, DPN-related sensory loss, gait dysfunction, ulceration risk, and pain can negatively affect daily function, mood, and quality of life [33]. Long-term complications should therefore be described not only through ulcers, falls, or amputations, but also through their effects on mobility, sleep, work capacity, emotional well-being, and overall quality of life.

The long-term burden of DPN is often shaped by overlapping symptoms and phenotypes rather than by a single isolated complication. Painful and painless features may coexist: burning, stabbing, electric shock-like pain, allodynia, or paresthesia can occur alongside numbness, sensory loss, gait abnormalities, and postural instability, while DPN remains linked to a higher risk of diabetic foot ulcers and amputations [12]. Painful DPN may also become a functional and emotional burden when sleep, mood, daily activities, and quality of life are affected. Treatment expectations should therefore remain realistic: complete pain resolution is rare, and care should aim to reduce pain while improving daily functioning, quality of life, sleep, and mood [36]. This broader view supports strategies that combine pain management with foot protection, gait and balance assessment, daily functioning, and quality of life.

## 7. Treatment Strategies and Prevention of Disease Progression

### 7.1. General Treatment Goals and Metabolic Risk-Factor Control

DPN treatment should be presented not as management of a single symptom, but as a broader strategy to preserve daily functioning and prevent further harm. Care should combine glycaemic and metabolic risk-factor control, symptom treatment, foot care, lifestyle measures, and patient education or support, while acknowledging that established DPN is difficult to reverse and that many available therapies mainly relieve symptoms rather than restore nerve function [8]. In painful DPN, expectations should be discussed clearly: treatment aims include pain reduction and improvement in daily functioning, quality of life, sleep, mood, mobility, and self-care. Because complete pain freedom is uncommon, a meaningful response is usually better framed as partial pain reduction, commonly around 30–50%, together with improved function [36]. This supports individualized, multidimensional management focused on slowing progression, protecting the feet, preserving activity, and addressing mood or sleep problems when they contribute to the pain burden.

Management should also address modifiable metabolic and vascular factors that continue to affect vulnerable peripheral nerves. Glycemic control remains central, particularly early and in type 1 diabetes, where intensive treatment has stronger evidence for delaying neuropathy. In type 2 diabetes, glucose control alone appears less protective, so it should be combined with attention to metabolic syndrome components and other modifiable risks, including dyslipidemia, hypertension, obesity, smoking, and glycemic variability [7]. Prevention should not be reduced to a single HbA1c target; when safely possible, it also includes limiting large glucose excursions, treating blood pressure and lipid abnormalities, supporting weight management, encouraging feasible physical activity, and promoting smoking cessation. These measures should be presented as attempts to reduce metabolic and vascular stress on peripheral nerves and lower the risk of foot complications, without implying that established DPN will simply reverse [3].

### 7.2. Exercise, Rehabilitation, and Mobility Support

Treatment should also help patients remain active as safely as possible, because DPN can impair balance and gait and increase fall risk. Exercise and rehabilitation may support this goal through individually selected aerobic activity, strengthening, balance and gait training, sensorimotor or proprioceptive work, and physiotherapy focused on lower-limb function, postural stability, and fall-risk factors [15]. For patients, movement has practical value beyond physiology: safer standing and walking can protect everyday functioning and reduce mobility-related fear. Activity should therefore be prescribed individually, with attention to exercise type, intensity and progression, protective sensation, pain, severe foot deformity or peripheral vascular disease, cardiovascular risk, hypoglycemia, glucose monitoring, and the musculoskeletal and skin status of the feet [2]. The aim is not to push every patient harder, but to rebuild safe movement, support independence, and include physical activity within a long-term plan for mobility and foot safety.

### 7.3. Pharmacological, Topical, and Advanced Treatment Options

When pain disrupts sleep, mood, mobility, usual activities, or self-care, pharmacological treatment becomes an important part of painful DPN management. Commonly recommended oral options include duloxetine, pregabalin, gabapentin, and tricyclic antidepressants. Selection should consider comorbidities, adverse-effect risk, drug interactions, and cost, while management should still include foot care and lifestyle support because pharmacological treatment mainly addresses symptoms rather than reversing established DPN [8]. Treatment goals should remain realistic: a useful response is meaningful pain reduction with better sleep and daily function, not guaranteed pain freedom. Therapy should be individualized, reviewed over time, and adjusted according to efficacy, tolerability, renal or cardiovascular safety, and patient preference [36].

For patients with localized painful DPN or poor tolerance of oral treatment, topical pain relief may be considered instead of simply escalating systemic medication. Capsaicin 8% patches and, in selected cases, lidocaine 5% patches may be used when pain remains inadequately controlled or when oral options are limited by adverse effects, comorbidities, renal impairment, polypharmacy, or interaction risk [36]. High-concentration capsaicin systems deliver capsaicin locally to TRPV1-expressing cutaneous nerve fibers and may reduce pain with limited systemic exposure, although application-site pain, erythema, or burning may occur [24]. These treatments are best presented as adjuncts within an individualized plan, with realistic expectations and monitoring of whether pain relief improves comfort, sleep, and everyday function.

Management may also include pathogenesis-oriented approaches intended to influence the underlying neuropathy rather than pain alone. DPN involves interacting metabolic and vascular mechanisms, with hyperglycemia and dyslipidemia affecting neuronal axons, dorsal root ganglion neurons, Schwann cells, and the vascular system; related pathways include ROS accumulation, ATP loss, mitochondrial dysfunction, inflammatory signaling, polyol-pathway activation, and AGE formation [20]. These mechanisms provide the rationale for selected pathogenetically oriented therapies, including α-lipoic acid, benfotiamine, actovegin, and epalrestat. However, although these agents have shown evidence of benefit in some clinical settings and are authorized for DPN treatment in several countries, long-term pivotal trials are still needed to define their role as mono- or combination therapies [35]. Clinically, they should be discussed as possible adjuncts for selected patients, not as guaranteed disease-reversing treatments, while symptoms, sensory deficits, foot-related risk, mobility, and quality of life continue to be monitored.

When pain remains disabling despite metabolic optimization, oral medication, topical options, and rehabilitation, clinicians should reassess the whole clinical picture rather than simply add another treatment. This includes considering whether the pain phenotype is well defined, whether previous therapies were effective or tolerated, and whether sleep disturbance, anxiety, depressed mood, reduced movement, fall risk, or loss of protective sensation is increasing the patient's burden. In selected patients with refractory painful DPN, neuromodulation, including spinal cord stimulation, may be considered as an advanced option to reduce pain and improve function, particularly when conventional approaches have not provided adequate relief [9]. Even then, care should remain multidisciplinary, linking pain control with education, physiotherapy, psychological support, foot protection, and realistic functional goals.

### 7.4. Foot Protection, Patient Education, and Lifestyle Support

DPN care should remain centered on foot protection, because loss of protective sensation is a major driver of diabetic foot ulceration. Patient education should translate this risk into practical habits: daily foot checking, attention to cracks, skin breakdown, pressure areas, foreign objects or poor shoe fit, appropriate footwear, early reporting of new wounds or suspected ulceration, and regular foot assessment with timely podiatry, footwear, wound-care, or multidisciplinary foot-team support when needed [1]. This should not be framed as blaming the patient, because self-care is shaped by social determinants of health, including financial resources, education, social support, living circumstances, and access to care [33]. Education should therefore help patients, and when appropriate caregivers, understand what to watch for and when to seek help, while making foot protection a shared clinical responsibility.

The therapeutic plan should also consider the metabolic context in which peripheral nerves remain vulnerable. Nutrition should not be presented as a stand-alone "diet for neuropathy"; rather, dietary quality may influence DPN-related pathways through glycemic variability, insulin resistance, lipid metabolism, oxidative stress, inflammation, vascular health, body weight, and the gut–nerve axis, while direct clinical evidence in established DPN remains limited [27]. Anti-inflammatory, plant-rich dietary patterns, improved glycemic and lipid control, weight management when appropriate, and microbiota-oriented strategies can be discussed as supportive elements of prevention or secondary prevention, not as cures. Selected supplements, including α-lipoic acid and NAD+-related approaches, are also discussed as potential adjuncts against oxidative and metabolic injury, but diet alone has not been established as a sufficient prevention strategy and should be integrated with broader lifestyle and clinical care [21]. This cautious framing leads naturally into the current challenges and future perspectives of DPN care.

## 8. Current Challenges and Future Perspectives

Despite progress in understanding DPN, clinical care often still addresses neuropathy only after symptoms or disability have become apparent. DPN may present with sensory loss, neuropathic pain, gait dysfunction, ulceration risk, and reduced quality of life, while current management remains largely focused on symptom relief and control of glycaemic and broader metabolic risk factors rather than established disease modification [33]. Several available therapies are only partially effective or limited by adverse effects, underscoring the need for earlier recognition, individualized risk assessment, more sensitive markers of progression, and mechanism-based treatments aimed at preserving nerve function before mobility, protective sensation, and quality of life are further compromised [21].

A major challenge is explaining why DPN varies so markedly between patients. Peripheral nerve injury reflects overlapping metabolic and cellular disturbances rather than a single pathway, with hyperglycemia and dyslipidemia contributing to bioenergetic failure, mitochondrial dysfunction, oxidative stress, inflammation, vascular injury, and disrupted Schwann-cell–axon metabolic support [34]. This biological complexity is mirrored by clinical heterogeneity, as DPN may present as painful, painless, or mixed sensory phenotypes. Phenotype-aware assessment, including tools such as quantitative sensory testing, may therefore help characterize patients and monitor progression more precisely [12].

Pathogenesis-oriented pharmacotherapy aims to influence the underlying neuropathy and its clinical consequences rather than only relieve pain. Some agents have shown clinical benefit, but their long-term value as mono- or combination therapies still requires confirmation in pivotal studies [35]. Future progress should therefore build on current care while avoiding the assumption that promising mechanisms have already been translated into durable, widely applicable treatment strategies.

Earlier and more precise detection should extend, rather than replace, clinical assessment. Diagnosis still relies mainly on clinical history and neurological examination; vibration testing and 10-g monofilament assessment remain useful for evaluating large-fiber involvement and loss of protective sensation, although monofilament testing does not reliably detect early DPN. Risk assessment should also consider metabolic context, because DPN risk factors include hyperglycaemia severity and duration as well as obesity, dyslipidaemia, triglyceride burden, inflammation, and vascular injury [33]. Emerging neurophysiological biomarkers, including pain-related evoked potentials, nerve excitability testing, and microneurography, may help detect small-fiber or early large-fiber dysfunction and monitor progression more objectively. However, many of these approaches remain impractical for routine outpatient use and require validation, standardization, and integration into clinically usable models [11].

A further question is why neuropathy develops or progresses differently across patients even when diabetes-related risk factors appear broadly comparable. Genetic susceptibility may partly shape this variability, with reported variants involving oxidative stress, inflammation, glucose and lipid metabolism, vascular regulation, and neuronal function [26]. However, this should not be interpreted as genetic determinism, because genetic signals must be considered alongside glycaemic exposure, dyslipidaemia, obesity, and comorbid conditions. Future genetic, epigenetic, and phenotypic studies may refine risk stratification and support more mechanism-informed prevention or treatment strategies. For now, personalized medicine in DPN remains a promising direction rather than a routine standard and requires stronger validation and clinically practical tools [29].

The promise of biomarkers, phenotyping, and AI-assisted tools will matter most if they can be incorporated into routine DPN care rather than remain confined to specialist or research settings. Current diagnostic practice still depends on regular screening with clinical assessment, monofilament testing, and tuning-fork or vibration-based methods, while newer point-of-care devices and AI-driven decision-support systems may improve early detection, risk stratification, and workflow efficiency when feasible and properly validated [6]. Their value should be judged not only by diagnostic performance, but also by whether they help clinicians act sooner, explain risk more clearly, and connect patients with follow-up, education, and multidisciplinary support. Because patients may face high medication costs, complex treatment regimens, and limited access to specialists or advanced diagnostics, digital innovation should be simple, affordable, and integrated into practical care pathways rather than added as another layer of complexity [31].

Future DPN care should be meaningful in daily life, not only technically innovative. Progress will depend on care pathways that link earlier diagnosis, progression monitoring, metabolic and pain management, foot-ulcer risk assessment, education, rehabilitation, and multidisciplinary support involving diabetes, neurology, podiatry, physiotherapy, nursing, dietetic, exercise, and psychological expertise [7]. New biomarkers, drugs, devices, or algorithms should be judged useful only when they strengthen clinical assessment, physician–patient decision-making, and patient-centred goals. Future studies should therefore look beyond nerve signals or pain intensity alone and include outcomes that matter to patients, such as daily functioning, sleep, mood, quality of life, mobility, self-care, usual activities, and foot-ulcer risk [36].

## 9. Discussion

The evidence synthesized in this review supports viewing DPN as a progressive, length-dependent disorder rather than only as a list of sensory symptoms. Mechanistically, hyperglycemia, dyslipidemia, mitochondrial dysfunction, Schwann cell–axon support, vascular susceptibility, and glia–axon communication converge on bioenergetic failure in long peripheral axons, helping to explain the distal-to-proximal pattern of nerve injury [34]. Clinically, this biology is reflected in tingling, burning or electric pain, numbness, loss of proprioception, nocturnal worsening, and, in advanced stages, weakness, poor balance, and unsteadiness; painful DPN can also impair daily functioning and quality of life [22]. DPN should therefore be discussed as a progressive clinical problem in which pathophysiology, diagnosis, treatment, complications, and quality of life are closely connected.

Within this continuum, diagnosis should be treated not as a purely technical checkpoint, but as an opportunity to detect symptoms, signs, and risk before neuropathy becomes more advanced. In routine diabetes care, bedside assessment based on history, lower-limb neurological examination, foot inspection, sensory testing, ankle reflexes, the 10-g monofilament, and the 128-Hz tuning fork remains valuable because these methods are simple, non-invasive, and feasible in everyday practice [4]. However, because many bedside tools emphasize large-fiber signs, early small-fiber involvement may be missed, especially when pain, temperature abnormalities, sudomotor dysfunction, or autonomic changes are subtle or asymptomatic. Small-fiber assessment, sudomotor testing, and quantitative sensory methods may therefore complement clinical examination when early or subclinical involvement is suspected [16]. Earlier detection is most useful when it leads to timely prevention, monitoring, referral, or treatment aimed at delaying progression and reducing complications.

After diagnosis identifies risk, treatment should move from detection to practical goals: relieving neuropathic pain, preventing complications, and preserving function. Pharmacological therapy for painful DPN may reduce burning, stabbing, or electric-shock-like pain and the associated burden on sleep and mood, but available options mainly target symptoms and do not reverse established DPN; drug selection should therefore be individualized according to comorbidities, adverse-effect profiles, potential interactions, and cost [8]. Pain relief alone is incomplete if the patient still feels unsafe while standing or walking, has impaired balance, or remains at risk of falls. Physical rehabilitation, including balance-oriented, gait, strengthening, sensorimotor, and functional exercise-based interventions, can improve balance-related outcomes in some studies and should be considered alongside pain-directed treatment when painful DPN is present [15]. Together, these data support care that is both symptom-relieving and function-preserving.

Beyond pain relief, treatment should address the broader functional consequences of DPN and the risk of progressive disability. Current management mainly targets prevention and symptom relief through blood glucose control, modification of risk factors such as dyslipidemia, obesity, hypertension, and smoking, lifestyle and pharmacological interventions, and pain-directed therapies, because no FDA-approved pathogenetically oriented pharmacological treatment reverses established DPN [2]. This limitation is important because DPN reflects interacting metabolic, inflammatory, microvascular, and neuronal processes rather than a single pathway, and these processes may differ across subtypes and stages. Future strategies should move toward mechanism-informed stratification, using validated phenotypes, biomarkers, and risk profiles to guide targeted interventions, while recognizing that many personalized approaches still require clinical validation before routine use [29]. The practical goal is to translate mechanistic insight into coordinated, patient-centered care that links symptom relief, prevention, risk-factor management, and functional support.

In practical terms, these findings argue against reducing DPN care to a single test, drug, or educational intervention. Patients need a care pathway that connects DPN recognition with pain management, metabolic risk reduction, exercise- or rehabilitation-oriented support, foot-risk prevention, psychological care, and patient education [33]. This is especially important because painful DPN is associated with impaired daily functioning, depression, sleep disturbance, financial instability, and reduced quality of life, while treatment success often means meaningful pain reduction rather than complete pain freedom [36]. Taken together, this perspective connects mechanisms, symptoms, diagnosis, complications, treatment, and future directions into a coherent clinical discussion. The central conclusion is that DPN requires integrated, patient-centered care linking neuropathic symptom control with foot-risk prevention, mobility, daily functioning, and quality of life.

## 10. Conclusions

Diabetic peripheral neuropathy is a progressive, multifactorial, and length-dependent complication of diabetes that reflects interactions between metabolic, vascular, inflammatory, oxidative, mitochondrial, and neuronal–glial mechanisms. Although it often begins with subtle or unrecognized sensory changes, its clinical impact may extend from distal pain, tingling, burning, numbness, and loss of protective sensation to gait instability, foot deformity, ulceration, fall risk, and impaired independence. DPN should therefore be viewed not only as a disorder of sensation or neuropathic pain, but as a multidimensional condition affecting mobility, sleep, mood, daily functioning, foot safety, and overall quality of life.

Early recognition remains essential, particularly because DPN may be asymptomatic or difficult to identify in its initial stages. Regular screening, careful history-taking, focused neurological examination, sensory testing, foot inspection, and individualized risk assessment are central to detecting neuropathy before preventable complications develop. Clinicians should also remain attentive to clinical heterogeneity, including painful, painless, mixed, small-fiber, and large-fiber presentations, as well as atypical features requiring further evaluation or exclusion of alternative causes.

Current management should be realistic and patient centered. Available strategies mainly aim to reduce symptoms, slow progression, preserve function, and prevent complications rather than reliably reverse established nerve damage. Effective care therefore requires more than pharmacological pain treatment alone. Glycemic and broader metabolic risk-factor control, foot protection, rehabilitation, lifestyle support, patient education, and attention to sleep, mood, mobility, and self-care should be integrated into individualized treatment. Multidisciplinary cooperation between diabetes care, neurology, podiatry, physiotherapy, nursing, dietetic, exercise, and psychological support may help address the full clinical burden of DPN.

Future progress will depend on earlier detection, improved risk stratification, and treatment personalization. Validated biomarkers, practical tools for assessing small-fiber and early nerve dysfunction, phenotype-aware approaches, and better integration of clinical, metabolic, genetic, and functional information may support more precise care. However, these approaches require further validation before routine use. The most important unmet need remains the development of safe and effective disease-modifying therapies that preserve nerve function and reduce the long-term burden of DPN on patients' daily lives.

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