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Review Article

Mechanisms of Small Fiber Degeneration in Neuropathic Pain Development of Diabetic Peripheral Neuropathy

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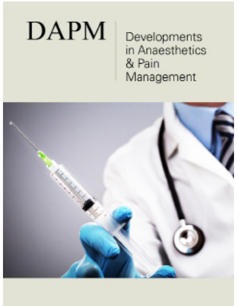

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Abstract

Background: Diabetic Peripheral Neuropathy (DPN) is one of the most common and debilitating complications of diabetes, characterized by progressive damage to peripheral nerves. Among the earliest pathological changes is the degeneration of small unmyelinated C-fibers and thinly myelinated Aδ-fibers, which are crucial for pain and temperature perception. Small fiber degeneration plays a central role in the transition from metabolic disturbances to clinical neuropathic pain.

Objective: This review aims to explore the underlying mechanisms contributing to small fiber degeneration in DPN and their role in the pathogenesis of neuropathic pain.

Methods: Relevant literature was reviewed from experimental, clinical and translational studies focusing on small fiber pathology, metabolic dysfunction and pain mechanisms in diabetic neuropathy.

Result: Multiple interrelated mechanisms contribute to small fiber degeneration. Chronic hyperglycemia induces oxidative stress, Advanced Glycation End-Product (AGE) accumulation and mitochondrial dysfunction, leading to axonal injury. Vascular insufficiency and impaired neurotrophic support further exacerbate fiber loss. Additionally, low-grade inflammation and immune-mediated processes sensitize nociceptors, promoting spontaneous firing and hyperexcitability. Structural changes such as reduced Intraepidermal Nerve Fiber Density (IENFD), altered ion channel expression and impaired axonal transport are strongly associated with pain phenotypes in DPN. These mechanisms collectively disrupt nociceptive signal processing, resulting in allodynia, hyperalgesia and spontaneous pain.

Conclusion: Small fiber degeneration represents a pivotal mechanism in the pathophysiology of painful DPN. Understanding the interplay between metabolic, vascular, inflammatory and neurotrophic factors provides critical insights into disease progression and pain generation. Targeting small fiber preservation and regeneration may open new therapeutic avenues for managing neuropathic pain in diabetes.

Keywords: Diabetic peripheral neuropathy; Small fiber neuropathy; Neuropathic pain; Intraepidermal nerve fiber density; Oxidative stress; Hyper excitability

Introduction

Diabetes mellitus is a global health concern with rising prevalence, affecting more than 500 million individuals worldwide [1]. Among its chronic complications, Diabetic Peripheral Neuropathy (DPN) is one of the most common and disabling, affecting up to 50% of patients with long-standing diabetes. DPN manifests with a wide spectrum of sensory and motor deficits, with neuropathic pain being a particularly distressing and challenging clinical problem. Painful DPN significantly impairs quality of life, functional independence and mental health and it is associated with increased healthcare costs and morbidity [2]. A hallmark of early diabetic neuropathy is small fiber degeneration, involving the unmyelinated C-fibers and thinly myelinated Aδ-fibers that mediate pain, temperature sensation and autonomic functions [3]. Loss of these fibers not only contributes to sensory deficits but also underlies the development of neuropathic pain [4]. Clinical studies consistently demonstrate a reduction in Intraepidermal Nerve Fiber Density (IENFD) in patients with painful DPN, correlating with symptom severity. Unlike large fiber involvement, which leads to numbness and motor impairment, small fiber pathology is strongly linked to spontaneous pain, allodynia and hyperalgesia [5].

The mechanisms driving small fiber degeneration in diabetes are complex and multifactorial. Persistent hyperglycemia initiates metabolic disturbances, including oxidative stress, Advanced Glycation End-Product (AGE) accumulation and impaired mitochondrial function. These metabolic insults trigger axonal damage and sensory neuron dysfunction, further aggravated by reduced neurotrophic support, microvascular ischemia and chronic low-grade inflammation. Altered ion channel expression and aberrant excitability of nociceptors exacerbate pain perception. Together, these processes result in structural and functional changes that underlie neuropathic pain generation [6]. Despite advances in understanding DPN, treatment options remain limited, often providing only partial symptomatic relief. Current pharmacological therapies such as pregabalin, duloxetine and gabapentinoids target symptom modulation rather than addressing the underlying degenerative mechanisms. Therefore, investigating the pathophysiology of small fiber degeneration is crucial for identifying novel therapeutic strategies aimed at neuroprotection, fiber regeneration and disease modification [7]. This review discusses the current knowledge on the mechanisms of small fiber degeneration in DPN and its role in neuropathic pain development [8]. By integrating evidence from experimental, clinical and translational research, we aim to highlight the interplay between metabolic, vascular, inflammatory and neurotrophic pathways in small fiber pathology and to explore their implications for future treatment approaches [9].

Mechanisms of Small Fiber Degeneration in Neuropathic Pain Development in Diabetic Peripheral Neuropathy

Metabolic dysfunction and oxidative stress

One of the earliest and most critical events in small fiber degeneration is the persistent metabolic disturbance caused by chronic hyperglycemia. Excess glucose enters alternative metabolic pathways, such as the polyol pathway, where aldose reductase converts glucose into sorbitol. Sorbitol accumulation not only exerts osmotic stress on neurons but also consumes NADPH, depleting the cell's antioxidant reserves (notably reduced glutathione). This renders small fibers highly vulnerable to oxidative injury [8]. In addition, chronic hyperglycemia accelerates the formation of Advanced Glycation End-Products (AGEs), which modify structural proteins, enzymes and receptors. AGEs bind to their receptor (RAGE) on neurons, Schwann cells and endothelial cells, activating pro-inflammatory transcription factors such as NF-κB. The result is a vicious cycle of oxidative stress and inflammation that progressively damages axons [9]. Mitochondrial dysfunction further amplifies this injury. Excess intracellular glucose increases electron leakage from the mitochondrial electron transport chain, producing Reactive Oxygen Species (ROS). Mitochondrial DNA damage and impaired ATP synthesis compromise axonal energy supply, leading to axonal swelling, fragmentation and degeneration.

Microvascular insufficiency and ischemia

Small fibers are particularly vulnerable to microvascular insufficiency because of their distal location and high metabolic demand. In diabetes, endoneurial blood vessels undergo structural changes, including basement membrane thickening, endothelial hyperplasia and capillary occlusion. These changes reduce endoneurial blood flow and impair oxygen delivery [10]. Endothelial dysfunction further contributes by decreasing Nitric Oxide (NO) bioavailability, impairing vasodilation. The resultant endoneurial hypoxia leads to ischemic injury of small fibers, exacerbating oxidative stress and energy failure. Ischemia not only accelerates axonal degeneration but also sensitizes nociceptors, producing ischemia-related pain.

Impaired neurotrophic support

The maintenance and survival of nociceptive small fibers critically depend on neurotrophic factors, particularly Nerve Growth Factor (NGF). In diabetes, both the synthesis and retrograde transport of NGF are impaired. This deficiency compromises nociceptor survival, axonal regeneration and synaptic maintenance. Other neurotrophins such as Brain-Derived Neurotrophic Factor (BDNF) and insulin-like growth factor-1 (IGF-1) are also reduced in diabetes. The impaired signaling through their receptors (TrkA, TrkB, IGF-1R) deprives neurons of vital regenerative cues. As a result, Intraepidermal Nerve Fiber Density (IENFD) progressively declines, correlating strongly with both pain intensity and sensory deficits in DPN [11].

Immune-mediated and inflammatory mechanisms

Low-grade chronic inflammation plays an important role in the degeneration of small fibers. Hyperglycemia activates innate immune pathways, triggering the release of pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) from macrophages, Schwann cells and mast cells within peripheral nerves [12]. These cytokines directly sensitize nociceptors by upregulating ion channels such as TRPV1 and voltage-gated sodium channels. Chemokines such as MCP-1 and CXCL12 further recruit immune cells, creating a neuroinflammatory microenvironment that perpetuates nerve damage. Over time, this inflammatory milieu not only accelerates fiber loss but also enhances neuronal hyperexcitability, leading to symptoms such as allodynia and hyperalgesia.

Ion channel dysfunction and hyperexcitability

A defining feature of neuropathic pain in DPN is the aberrant excitability of small fibers, driven by altered expression and function of ion channels.

a. **Sodium channels:** Upregulation of Nav1.7, Nav1.8 and Nav1.9 sodium channels in nociceptors produces ectopic discharges and spontaneous firing. Gain-of-function mutations in Nav1.7 have been directly linked with painful neuropathies.

b. **Calcium channels:** Dysregulation of Cav3.2 and Cav2.2 calcium channels contributes to abnormal excitatory neurotransmitter release, sustaining pain signaling.

c. **Potassium channels:** Downregulation of Kv channels impairs membrane repolarization, prolonging nociceptor excitability.

d. **TRP channels:** TRPV1 (heat-sensitive) and TRPA1 (oxidative stress-sensitive) are upregulated, amplifying nociceptor sensitivity to thermal and chemical stimuli.

These changes create a state of peripheral sensitization, where even minor stimuli generate exaggerated pain responses.

Structural and functional small fiber changes

Progressive loss of Intraepidermal Nerve Fiber Density (IENFD) is a hallmark pathological feature of DPN. Skin biopsies consistently demonstrate reduced IENFD in patients with painful DPN, correlating with symptom severity [13]. Axonal transport deficits also contribute, as diabetes disrupts the transport of essential proteins, organelles and mitochondria. This leads to a "dying-back" neuropathy, where distal axons degenerate first. In some cases, aberrant reinnervation and maladaptive sprouting occur, creating abnormal connections that contribute to spontaneous pain.

Central sensitization and neuroplasticity

While peripheral mechanisms initiate neuropathic pain, central changes in the spinal cord and brain sustain and amplify it. Persistent input from degenerating small fibers induces hyperexcitability of dorsal horn neurons, with reduced inhibitory neurotransmission (GABA, glycine) [14]. Functional MRI studies demonstrate cortical reorganization, with altered activity in the primary somatosensory cortex and pain-related networks. This central sensitization explains why pain often persists even when peripheral damage stabilizes.

Integration of mechanisms

The degeneration of small fibers in DPN results from a complex interplay of metabolic, vascular, inflammatory, neurotrophic and ion channel-related mechanisms. These mechanisms reinforce one another in a vicious cycle: hyperglycemia triggers oxidative stress and mitochondrial dysfunction, vascular insufficiency worsens ischemia, impaired neurotrophic support reduces repair capacity, inflammation enhances degeneration and ion channel changes drive pain hypersensitivity [15]. The end result is progressive loss of small fibers and persistent neuropathic pain, which remains one of the most challenging complications of diabetes to treat.

Clinical Evidence for Small Fiber Degeneration in Painful Diabetic Neuropathy

Skin biopsy and intraepidermal nerve fiber density (IENFD)

One of the strongest clinical markers of small fiber degeneration is the reduction in Intraepidermal Nerve Fiber Density (IENFD), assessed through skin biopsy and immunostaining with protein gene product 9.5 (PGP9.5). Studies consistently demonstrate that patients with painful DPN show significantly lower IENFD compared to painless DPN or diabetic patients without neuropathy. Importantly, IENFD correlates with both the severity of neuropathic pain and Quantitative Sensory Testing (QST) abnormalities [7].

a. **Supporting evidence:** A large multicenter study showed that patients with painful DPN had markedly reduced IENFD at the distal leg compared to both non-painful DPN and control groups.

b. **Clinical relevance:** Reduced IENFD provides an objective diagnostic marker for small fiber pathology and is included in consensus criteria for small fiber neuropathy diagnosis.

Quantitative sensory testing (QST)

QST provides functional evidence of small fiber damage by assessing thresholds for temperature, vibration, and mechanical stimuli. Patients with painful DPN often demonstrate thermal hypoesthesia (loss of heat/cold detection) combined with mechanical and thermal hyperalgesia, reflecting small fiber dysfunction and sensitization [9].

a. **Clinical findings:** Altered cold detection thresholds and heat-pain thresholds are among the most consistent abnormalities in painful DPN.

b. **Interpretation:** This dual pattern of loss (hypoesthesia) and gain (hyperalgesia) of sensory function reflects both fiber degeneration and aberrant excitability of surviving nociceptors.

Corneal confocal microscopy (CCM)

Corneal Confocal Microscopy (CCM) has emerged as a non-invasive imaging technique to visualize small fiber pathology in vivo. Corneal Nerve Fiber Length (CNFL), density and branching are significantly reduced in patients with painful DPN [13].

a. **Clinical evidence:** Several cross-sectional and longitudinal studies have shown that CNFL reduction correlates with neuropathic pain severity and disease progression.

b. **Advantages:** Provides a non-invasive, reproducible tool to monitor small fiber degeneration, potentially replacing invasive biopsies in clinical trials.

Electrophysiological and neurophysiological studies

Standard nerve conduction studies primarily assess large fibers and often appear normal in early DPN. However, specialized techniques provide evidence of small fiber dysfunction:

a. **Laser-evoked potentials (LEPs):** Demonstrate delayed or absent cortical responses in painful DPN, consistent with C-fiber dysfunction.

b. **Microneurography:** Direct recordings reveal abnormal spontaneous discharges of nociceptors in painful DPN.

c. **Contact heat evoked potentials (CHEPs):** Show impaired small fiber conduction correlating with pain severity.

These methods provide strong physiological evidence linking small fiber degeneration and hyperexcitability to neuropathic pain.

Biomarker evidence

Serum and tissue biomarkers provide indirect support for small fiber involvement:

i. Elevated inflammatory cytokines (TNF-α, IL-6, MCP-1) in painful vs. painless DPN.

ii. Reduced NGF and BDNF levels correlate with decreased IENFD and pain intensity.

iii. Increased oxidative stress markers (8-OHdG, malondialdehyde) in patients with painful neuropathy.

Such findings align with mechanistic studies, reinforcing the role of metabolic, inflammatory and neurotrophic pathways in small fiber degeneration.

Longitudinal and interventional studies

Longitudinal studies demonstrate that small fiber degeneration precedes and predicts the onset of neuropathic pain in diabetes. In some patients, painful symptoms develop even when large fiber tests remain normal, underscoring the primary role of small fibers [14].

a. Intervention evidence: Clinical trials with agents such as alpha-lipoic acid and epalrestat (aldose reductase inhibitor) show modest improvements in IENFD and pain scores, suggesting that preserving small fibers can reduce neuropathic pain [15].

b. Lifestyle interventions: Exercise and strict glycemic control have been shown to slow small fiber loss and improve sensory function.

Integration of clinical evidence

Taken together, clinical data strongly support small fiber degeneration as the key pathological substrate for neuropathic pain in DPN. Objective structural measures (IENFD, CCM), functional testing (QST, LEPs) and biochemical markers converge to demonstrate that metabolic, vascular, inflammatory and neurotrophic imbalances manifest clinically as loss of intraepidermal nerve fibers, altered nociceptor excitability, and neuropathic pain [16].

Therapeutic Implications

Understanding the mechanisms that drive small-fiber degeneration in Diabetic Peripheral Neuropathy (DPN) directly shapes rational therapeutic strategies. Interventions may be grouped into: (A) symptomatic pain control, (B) mechanism-directed disease modification and neuroprotection, (C) regenerative and neuromodulatory approaches and (D) multidisciplinary/rehabilitative strategies that improve function and quality of life. Below I summarize each category, link therapies to the underlying pathophysiology, note practical considerations and suggest figures/tables for a textbook presentation [17].

Symptomatic pharmacologic therapies (pain control):

These agents do not reverse fiber loss but reduce pain by modulating nociceptive transmission or central sensitization.

A. First-line systemic agents

a) SNRIs (e.g., duloxetine) and gabapentinoids (pregabalin, gabapentin)-reduce central sensitization and aberrant excitability. They target abnormal dorsal horn processing and reduce ectopic discharge perception.

b) Practical note: Titrate to effect and monitor side effects (sedation, dizziness, GI effects, blood pressure changes).

B. Second-line/adjunctive agents

a) Tricyclic antidepressants (amitriptyline, nortriptyline)-effective but limited by anticholinergic/cardiac side effects.

b) Opioids / tramadol-short-term benefit in refractory cases; long-term use is limited by tolerance, dependence and adverse effects.

C. Topical therapies

a) High-concentration capsaicin patch (8%)-depletes substance P and desensitizes nociceptors; useful for localized painful areas.

b) Lidocaine 5% patch-reduces ectopic firing locally with minimal systemic effects.

c) Practical note: Topicals are helpful when pain is focal and systemic agents are contraindicated.

Mechanism-directed disease modification & neuroprotection

These approaches aim to interrupt the pathogenic cascade (hyperglycemia→oxidative stress→ischemia→trophic factor loss→degeneration) and thereby slow or reverse small fiber loss [18].

A. Glycemic control

a) Tight glycemic control remains foundational to slow progression of DPN; it reduces metabolic stress and downstream oxidative injury.

b) Practical note: Benefits are greater when instituted early; balance intensive control against hypoglycemia risk.

B. Antioxidant and metabolic modulators

a) Alpha-Lipoic Acid (ALA): An antioxidant shown in some trials to improve symptoms and possibly small fiber function through ROS scavenging and mitochondrial protection.

b) Aldose reductase inhibitors (e.g., epalrestat in some regions): Reduce polyol pathway flux and sorbitol accumulation, preserving NADPH and antioxidant capacity.

c) Practical note: These agents address metabolic drivers of axonal injury; efficacy may be modest and vary by agent.

C. **Improving microvascular perfusion**

a) Strategies that improve endothelial function and microcirculation (exercise, control of dyslipidemia and hypertension, smoking cessation) reduce ischemic stress on small fibers.

D. **Enhancing neurotrophic support**

a) Approaches aimed at restoring NGF/BDNF/IGF-1 signaling are under study. Exogenous NGF showed biologic promise but was limited by side effects; downstream modulation of trophic pathways remains an active research area.

Regenerative and neuromodulatory approaches

Target the injured nerve environment to promote regeneration or modulate aberrant excitability.

A. **Regenerative strategies**

a) Cell therapies (stem/progenitor cells): Aim to provide trophic support, modulate inflammation and encourage regeneration. Preclinical studies are promising; clinical translation is ongoing.

b) Growth factor therapies: Local or systemic delivery of neurotrophins (e.g., NGF analogs) to promote fiber regeneration-conceptually attractive but challenged by delivery, dosing and side effects.

B. **Neuromodulation**

a) Peripheral neuromodulation/TENS: Noninvasive, may reduce pain via gate control and activation of descending inhibitory pathways.

b) Spinal cord stimulation (SCS): Effective in refractory neuropathic pain; can modify dorsal column signaling and reduce central sensitization.

c) Noninvasive brain stimulation (rTMS, tDCS): Experimental approaches to modulate cortical pain networks and reduce central sensitization.

d) Practical note: Neuromodulation options are considered for refractory, severe pain after conservative measures fail.

Rehabilitation, lifestyle and psychosocial interventions

These approaches are essential adjuncts that address the systemic contributors to DPN and improve patient outcomes [16].

A. **Exercise and physical therapy**

i. Aerobic and resistance exercise improve glycemic control, enhance microvascular perfusion, reduce oxidative stress and may promote neuroplasticity and symptomatic improvement.

ii. Balance, gait training and foot care reduce fall and ulceration risk.

B. **Foot care and injury prevention**

i. Regular inspection, footwear optimization and patient education are crucial since small-fiber loss predisposes to painless injury and ulcers.

C. **Psychological therapies**

i. Cognitive Behavioral Therapy (CBT), mindfulness and pain-coping interventions reduce pain catastrophizing and improve quality of life; important for central mechanisms of chronic pain.

Precision and future-oriented strategies

Translational insights into ion-channel alterations, immune pathways and molecular drivers enable more targeted therapies.

A. **Ion channel–targeted drugs**

i. Selective blockers or modulators of Nav1.7/Nav1.8, Cav, or TRP channels aim to reduce ectopic firing at the nociceptor level with fewer systemic effects.

B. **Immunomodulation**

i. Therapies that selectively reduce neuroinflammation (e.g., cytokine modulators) could limit degeneration while preserving host defense.

C. **Biomarker-driven, personalized care**

i. Use of skin biopsy, corneal confocal microscopy, and molecular biomarkers to stratify patients (e.g., degenerative vs. predominantly hyperexcitable phenotypes) and guide therapy selection.

D. **Gene therapy and novel delivery systems**

i. Approaches to correct channelopathies, upregulate trophic factors, or silence pathologic signaling are experimental but conceptually powerful.

Practical recommendations for clinicians and researchers

i. Combine early diagnosis (IENFD/CCM/QST) with aggressive risk factor modification (glycemia, lipids, BP, smoking cessation) to slow structural loss.

ii. Use evidence-based symptomatic agents as first-line for neuropathic pain and personalize choice based on comorbidities and side-effect profiles.

iii. Incorporate rehabilitation, exercise and psychological support as standard components of care.

iv. Advocate for and enroll patients in mechanism-driven clinical trials (neuroprotective, regenerative, channel-targeted) to accelerate translation.

v. For researchers: focus on translational endpoints (IENFD, corneal nerve metrics, validated QST measures, and molecular biomarkers) to link pathophysiologic target engagement with clinical outcomes.

Discussion

Diabetic peripheral neuropathy remains one of the most common and disabling complications of diabetes, with small-fiber degeneration as a central pathological hallmark [17]. The mechanisms underlying this process are multifactorial and interdependent, reflecting the cumulative impact of metabolic, vascular, inflammatory and neurotrophic disturbances. Chronic hyperglycemia drives polyol pathway activation, oxidative stress and mitochondrial dysfunction, which in turn impair axonal energy supply and structural integrity [18]. Simultaneously, microvascular insufficiency reduces oxygen and nutrient delivery, while immune activation and pro-inflammatory cytokines amplify axonal injury. Loss of neurotrophic factors such as NGF, BDNF and IGF-1 further compromises regenerative capacity, whereas ion-channel dysfunction contributes to ectopic discharges and neuropathic pain [19]. Clinical evidence from skin biopsy, corneal confocal microscopy and quantitative sensory testing underscores the strong correlation between small-fiber pathology and the severity of neuropathic symptoms. Longitudinal data suggest that fiber loss not only explains sensory deficits but also predicts the development of chronic pain syndromes and functional impairment. These insights highlight the importance of early detection of small-fiber involvement as both a diagnostic marker and a therapeutic window [20]. Sirtuin is critical to the prevention of insulin resistance, metabolic dysregulation, mitophagy, vascular and inflammatory processes [21]. Sirtuin 1 responsible is responsible for the regulation of neurotrophic factors such as brain derived neurotrophic factor, insulin like growth factor-1, neuropeptide y and nerve growth factor [22]. Sirtuin 1 is important to neuron development and promoting axon growth and protecting against axonal degeneration. The role of Sirtuin 1 activators versus inhibitors are critical to the treatment of diabetic peripheral neuropathy [23]. Therapeutically, current approaches are largely symptomatic, with duloxetine, pregabalin, and gabapentin forming the mainstay of pharmacologic management. Topical agents such as lidocaine and capsaicin provide localized relief, while non-pharmacologic modalities like exercise, physiotherapy, and neuromodulation serve as valuable adjuncts [20]. However, these treatments do not halt disease progression. Mechanism-based therapies such as antioxidants (e.g., alpha-lipoic acid), aldose reductase inhibitors and agents improving microvascular function offer a disease-modifying rationale, though clinical efficacy remains variable. Emerging avenues-including ion channel modulators, regenerative cell-based therapies, neurotrophin supplementation and personalized biomarker-driven strategies-hold promise for addressing the root causes of small-fiber degeneration [2].

Conclusion

In conclusion, small-fiber degeneration in DPN is the result of a complex interplay of metabolic and vascular insults, immune dysregulation and impaired neurotrophic support. The progression from asymptomatic fiber loss to debilitating neuropathic pain reflects a continuum in which early mechanisms feed into chronic maladaptive plasticity. An integrative therapeutic approach-combining optimal metabolic control, mechanism-targeted agents, symptomatic management and rehabilitative strategies-is therefore essential. Future research should focus on precision medicine guided by molecular and structural biomarkers, aiming not only to alleviate pain but also to preserve and regenerate small fibers. Such a paradigm shift has the potential to transform the outlook of patients living with diabetic neuropathy from inevitable decline toward sustained functional recovery.

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