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DECODING DIABETIC PERIPHERAL NEUROPATHY: PATHOGENESIS, DIAGNOSTIC BREAKTHROUGHS, AND EMERGING THERAPEUTICS- A COMPREHENSIVE REVIEW

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Abstract:
Diabetic Peripheral Neuropathy (DPN) is a common and debilitating complication of diabetes, characterized by peripheral nerve dysfunction after excluding other potential causes. Diabetic distal symmetric polyneuropathy (DSPN) is the most prevalent form, affecting 10-15% of newly diagnosed Type 2 Diabetes Mellitus (T2DM) patients, with prevalence rates exceeding 50% in those with more than 10 years of diabetes. The primary symptoms include bilateral limb pain, numbness, and paresthesia, which in severe cases can lead to foot ulcers and even amputation. Although the precise pathogenesis remains incompletely understood, hyperglycemia, lipid metabolism disturbances, and insulin signaling abnormalities are recognized as key contributors, initiating a cascade of pathophysiological changes that affect myelinated and unmyelinated nerve fibers, perikaryon, neurovascular structures, and glial cells. Moreover, impaired insulin signaling inhibits axonal repair and promotes neuronal apoptosis. Recent studies have uncovered several mechanisms underlying DPN, including oxidative stress, microvascular damage, neuroinflammation, mitochondrial dysfunction, and cellular oxidative damage. Additionally, a reduced oxygen supply through vasa nervorum and inflammatory processes further exacerbate nerve injury. The most common clinical presentation is symmetrical painful neuropathy, especially affecting the lower limbs. Understanding the interactions between these mechanisms is crucial for advancing diagnostic and therapeutic strategies. This review synthesizes the latest research on DPN's pathophysiology and diagnostic challenges, offering novel insights into the disease's underlying mechanisms and the potential for targeted interventions to improve patient outcomes.

Keywords: Apoptosis; Diabetic Peripheral Neuropathy; Foot ulcers; Neuroinflammation; Type 2 Diabetes Mellitus

1. Introduction

Diabetic neuropathy (DN) is one of the most prevalent and debilitating chronic complications of diabetes mellitus (DM), affecting a significant portion of the diabetic population worldwide [1]. Diabetic peripheral neuropathy (DPN) is the most common type of diabetic neuropathy (DN), affecting a substantial portion of the diabetic population. Studies suggest that approximately half of all individuals with diabetes are likely to experience DPN at some point in their lives. The condition typically presents as distal symmetric polyneuropathy, characterized by bilateral numbness, sensory loss, and tingling sensations in the extremities [2]. In some cases, patients experience neuropathic pain, which can be described as sharp, burning, or electrical in nature [3]. Over time, DPN may progress to severe complications such as foot ulcers and, in extreme cases, non-traumatic lower limb amputations. The incidence of DPN increases with the duration of diabetes, and it is one of the leading causes of disability and reduced quality of life among individuals with long-term diabetes [4]. In fact, DPN is a major contributor to healthcare costs globally, with estimates in the United States suggesting that the annual cost of treating painful DPN and its complications, such as foot ulcers [5, 6] and amputations, ranges from $4 billion to $13 billion [7].

The exact pathogenesis of DPN remains incompletely understood; however, it is widely accepted that hyperglycemia, dyslipidemia, and insulin resistance are

central to the development of the condition. These metabolic disturbances trigger a cascade of detrimental effects on the peripheral nervous system, including mitochondrial dysfunction, oxidative stress, neuroinflammation, and alterations in neuronal-glial cell function. Hyperglycemia, in particular, exacerbates these processes by inducing advanced glycation end-products (AGEs) that damage blood vessels, leading to impaired microvascular circulation, which in turn affects nerve function. In addition, chronic exposure to elevated blood glucose levels disrupts the integrity of the axonal and myelin structures, impairing nerve signal transmission. Furthermore, the insulin resistance characteristic of type 2 diabetes inhibits the regenerative capacity of peripheral nerves and promotes neuronal apoptosis [8–10].

Aside from these intrinsic metabolic factors, some commonly prescribed medications for diabetes, such as proton pump inhibitors and metformin, have been identified as potential contributors to the development or worsening of DPN. These drugs can induce vitamin B12 deficiency, which is a known risk factor for neuropathy, further complicating the management of the condition [11].

The prevalence of diabetes and, consequently, DPN continues to rise globally, with current estimates suggesting that over 500 million people worldwide suffer from diabetes. Projections indicate that this number could grow to 700 million by 2045. As the number of individuals affected by DPN increases, early detection and effective management become more crucial [12]. Timely intervention can prevent the progression of DPN, potentially avoiding severe outcomes such as ulcers and amputations. Early and accurate diagnosis is essential, and emerging diagnostic tools, including more sensitive nerve conduction tests, are improving the ability to detect neuropathy at earlier stages [13–15].

This review aims to provide a comprehensive overview of the most recent advances in the understanding of DPN, including its pathophysiology, clinical manifestations, diagnostic challenges, and therapeutic strategies. By synthesizing current research on the mechanisms underlying DPN and exploring novel approaches to diagnosis and treatment, this paper seeks to offer insights into the future of DPN management, with the goal of improving patient outcomes and reducing the burden of this widespread and costly complication of diabetes.

2. Pathogenesis of Diabetic Peripheral Neuropathy

Diabetic Peripheral Neuropathy (DPN) is a severe complication of diabetes mellitus, resulting from prolonged hyperglycemia and leading to peripheral nerve damage. Its pathogenesis is multifaceted, involving intricate metabolic and intracellular mechanisms that remain only partially understood.(16–19). This section explores the key mechanisms underlying the development and progression of DPN, highlighting the cellular, molecular, and systemic pathways involved in neuropathic damage associated with diabetes.

2.1. Disruption of the Blood-Nerve Barrier (BNB)

The blood-nerve barrier (BNB) plays a pivotal role in maintaining the homeostasis of peripheral nerves by regulating the transport of nutrients, electrolytes, and other essential molecules. The structural integrity of the BNB relies on endothelial cells, pericytes, and basal lamina [20, 21]. In diabetes, hyperglycemia impairs the function of the BNB, leading to increased permeability and the leakage of high-molecular-weight proteins, such as albumin and immunoglobulins, into the nerve parenchyma.

Alterations in BNB function are considered an early event in DPN pathogenesis. Elevated glucose levels activate the polyol pathway, disrupting cell membrane permeability and impairing the regulation of protein and electrolyte transport. This disturbance contributes to nerve edema, which can exacerbate ischemic damage [22,23]. Additionally, endothelial cell swelling, basal lamina thickening, and the accumulation of fibrin further contribute to vascular narrowing, reducing blood flow to nerve tissues and promoting oxidative stress and inflammation. This ischemic environment can initiate a cascade of events leading to nerve degeneration [24].

2.2. Inflammatory Responses and Oxidative Stress

Chronic hyperglycemia is associated with systemic inflammation, which significantly contributes to the pathogenesis of DPN. Elevated blood sugar levels induce the activation of pro-inflammatory pathways, such as the cyclooxygenase-2 (COX-2) pathway [25], which exacerbates oxidative stress in peripheral nerves. Inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1beta (IL-1β), are known to mediate nerve injury by promoting the activation of macrophages and glial cells, further enhancing local inflammation [26, 27].

Oxidative stress, characterized by the overproduction of reactive oxygen species (ROS), is another key factor in DPN. ROS contribute to lipid peroxidation, protein modification, and mitochondrial dysfunction, all of which lead to cellular damage. Studies have demonstrated that decreased antioxidant activity in patients with diabetes is associated with an increased risk of developing DPN. Superoxide dismutases (SODs) and glutathione (GSH), two crucial antioxidant molecules, are often found in reduced concentrations in individuals with DPN, highlighting the role of oxidative imbalance in the disease process [28,29].

2.3. Advanced Glycation End Products (AGEs)

Advanced glycation end products (AGEs), formed via the non-enzymatic glycosylation of proteins and lipids, are a defining feature of diabetic complications. In DPN, AGEs build up within nerve tissues, such as the myelin sheath and endoneurial microvessels. This accumulation activates the receptor for AGEs (RAGE) on neuronal surfaces, triggering intracellular signaling cascades involving the mitogen-activated protein kinase (MAPK) and phosphoinositide-3 kinase (PI3K) pathways [30]. This leads to the production of ROS, further exacerbating oxidative stress and contributing to neuronal damage.

AGEs also impair nerve function by inducing alterations in nerve morphology, reducing the efficiency of nerve conduction. Their interaction with RAGE on Schwann cells

and endothelial cells disrupts normal cellular function, promoting apoptosis and axonal degeneration. The accumulation of AGEs in the microvessels results in endothelial dysfunction and impaired blood flow to nerve tissues, contributing to ischemic damage and worsening neuropathy [31, 32].

2.4. Lipids and Dyslipidemia in DPN

Lipids play a significant role in the pathogenesis of DPN, particularly in the context of diabetes-induced dyslipidemia. In diabetes, elevated levels of free fatty acids and lipoproteins contribute to endothelial dysfunction, promoting inflammation and oxidative stress. The peroxidation of lipids, triggered by ROS, generates toxic byproducts that damage cellular membranes, including those of neurons [33]. This lipid-induced oxidative damage contributes to neuronal dysfunction and exacerbates the symptoms of DPN.

Moreover, recent studies have highlighted the disruption of lipid metabolism in individuals with DPN, particularly alterations in sphingolipid metabolism [34]. Sphingolipids, which are essential components of cell membranes, are involved in various signaling pathways that regulate cell growth, survival, and apoptosis [35]. Dysregulated sphingolipid metabolism in DPN may impair mitochondrial function and disrupt bioenergetics in peripheral nerves. This leads to reduced ATP production, mitochondrial dysfunction, and compromised nerve regeneration [36, 37].

2.5. Mitochondrial Dysfunction and Impaired Nerve Repair

Mitochondria are essential for maintaining cellular energy homeostasis, and their dysfunction is central to the pathogenesis of DPN. In the context of diabetes, mitochondrial overproduction of ROS leads to oxidative damage of mitochondrial proteins, lipids, and DNA. This mitochondrial dysfunction impairs the ability of neurons to generate ATP, which is crucial for maintaining normal neuronal function and promoting repair processes.

In addition to metabolic disturbances, mitochondrial dysfunction impairs the regeneration of damaged nerves. Schwann cells, which are responsible for myelination and nerve repair, rely heavily on mitochondrial function. In diabetic individuals, mitochondrial dysfunction in Schwann cells disrupts their regenerative capacity, contributing to the progression of DPN. This impairment of nerve repair mechanisms leads to axonal degeneration and the persistence of neuropathy.

2.6. Genetic and Epigenetic Factors

Genetic predisposition contributes to the risk of developing DPN. Variations in specific genes related to oxidative stress response, inflammation, and lipid metabolism can elevate the likelihood of neuropathy. For instance, polymorphisms in the angiotensin-converting enzyme (ACE) gene, methylenetetrahydrofolate reductase (MTHFR) gene, and genes linked to the pentose phosphate pathway have been associated with heightened susceptibility to DPN. Recent research has also explored the role of microRNAs (miRNAs) in DPN [38]. These small non-coding RNAs play a key role in regulating gene expression and are involved in various cellular processes such as inflammation, apoptosis, and insulin signaling. In DPN patients, specific miRNAs, such as miRNA-199a-3p and miRNA-128a, are upregulated, whereas others, like miRNA-155 and miRNA-499a, are downregulated [39]. Understanding the role of miRNAs in DPN may provide new insights into the molecular mechanisms underlying the disease and offer potential targets for therapeutic intervention.

2.7. Autoimmune Mechanisms in DPN

Although the primary pathophysiology of DPN is related to metabolic and vascular changes, autoimmune mechanisms have also been proposed as contributing factors. Some studies have observed an increased prevalence of antinuclear antibodies (ANA) and other autoimmune markers in individuals with DPN[40]. The presence of autoantibodies, such as those against the 65-kDa glutamic acid decarboxylase (GAD65)[41], has been associated with a higher risk of developing neuropathy, particularly in individuals with type 1 diabetes (T1DM) [42].

The autoimmune response may contribute to DPN through mechanisms such as the destruction of peripheral nerves or the activation of inflammatory pathways that damage nerve tissue. However, the exact role of autoimmunity in DPN remains unclear, and further studies are needed to confirm these findings and establish their clinical relevance [43].

3. Diagnosis and Treatment of Diabetic Peripheral Neuropathy (DPN)

3.1. Screening and Diagnosis of DPN

The screening process for Diabetic Peripheral Neuropathy (DPN) involves a thorough clinical evaluation, including an assessment of medical history and various sensory tests. These tests help identify potential neuropathy in diabetic patients by measuring ankle reflex, vibration, pressure, pain sensation, and temperature sensitivity. Standard tools used include:

- **Semmes-Weinstein Monofilament**: For testing light touch sensation.
- **Tiptherm Rod**: For evaluating temperature sensation.
- **Rydel-Seiffer Tuning Fork**: For vibration perception.
- **Pin-Prick Test**: To assess pain sensation [44].

In addition to these basic screening tests, several scoring systems can be employed to provide a standardized diagnosis of DPN, such as the Michigan Neuropathy Screening Instrument and Neuropathy Symptom Score [45]. These tools assess both neuropathic symptoms and signs, including the Neuropathy Disability Score.

When symptoms are atypical, further diagnostic procedures may include nerve conduction studies (NCS), quantitative sensory testing, and intraepidermal nerve fiber density measurements. More advanced imaging techniques, like tibial nerve T2 values obtained through magnetic resonance imaging (MRI), are emerging as non-invasive methods for monitoring DPN progression[44–48].

3.2. The Importance of Blood Sugar Control

Blood glucose management plays a pivotal role in the prevention and management of DPN. Elevated blood glucose levels are a known contributor to the development and progression of peripheral neuropathy. Studies have

shown that individuals with diabetes are significantly more likely to develop DPN, with the risk being approximately five times higher than in those with normal glucose levels.

Aggressive glycemic control is particularly effective in patients with Type 1 Diabetes (T1DM), showing significant improvements in nerve conduction and vibration perception [49, 50]. However, the benefits are more limited in Type 2 Diabetes (T2DM), especially in terms of NCS outcomes. In recent years, researchers have also explored the impact of metabolic syndrome (MetS) on DPN [51]. Conditions such as obesity, a major component of MetS, have been identified as independent risk factors for the development of neuropathy, even in non-diabetic obese individuals [52, 53]. Therefore, a multifaceted approach that includes weight management, exercise, and dietary modifications, in conjunction with glycemic control, is essential for managing DPN.

3.3. Pharmacological Treatments for DPN

Current pharmacological therapies aim to alleviate symptoms, particularly pain, as there are no drugs available to reverse the progression of DPN. Treatments can be categorized into two main groups:

- **Symptom-Alleviating Drugs**: These include anticonvulsants (e.g., pregabalin [54], gabapentin), tricyclic antidepressants (e.g., amitriptyline), and serotonin-noradrenaline reuptake inhibitors (e.g., duloxetine). Among these, gabapentin and pregabalin(55) are commonly used as first-line treatments for painful DPN[56].
- **Pathogenesis-Targeted Therapies**: These aim to address the underlying causes of DPN, including oxidative stress, impaired microcirculation, and neurotrophic deficiencies. Common medications in this category include methylcobalamin (for nerve regeneration) [57,58], alpha-lipoic acid (for combating oxidative stress)[59], and epalrestat (for inhibiting aldose reductase)[60].

While opioids can be effective for severe neuropathic pain, they are generally not recommended due to their long-term safety concerns and potential for addiction. Topical therapies such as the capsaicin 8% patch and lidocaine 5% patch have shown promise for pain relief, especially in cases where oral medications are less effective.

Combination therapies are also gaining attention, as they may offer improved efficacy with fewer side effects. For example, a combination of duloxetine and gabapentin has been shown to provide effective pain management for DPN patients [61–63].

3.4. Non-Pharmacological Treatments for DPN

Given the limitations of pharmacological treatments, non-pharmacological approaches are often used as adjuncts to therapy. While the evidence supporting these treatments is still evolving, several methods have demonstrated promise in improving symptoms and overall quality of life for DPN patients [64–67].

- **Psychological Support**: Mental health counseling can play a key role in managing chronic pain and the emotional burden associated with DPN.
- **Acupuncture and Physiotherapy**: These therapies have been used for centuries to alleviate pain and improve circulation, and modern studies suggest they can provide relief for some individuals with DPN.
- **Transcutaneous Electrical Nerve Stimulation (TENS)**: This technique uses low-voltage electrical currents to stimulate the nerves and reduce pain.
- **Spinal Cord Stimulation (SCS)**: For patients with chronic, refractory neuropathic pain, high-frequency (10 kHz) spinal cord stimulation has shown long-term efficacy and safety. Studies indicate that SCS can provide substantial relief for individuals whose pain is not controlled by medications.

3.5. Emerging Therapies and Future Directions

As research on DPN progresses, several promising therapies are emerging. These include gene therapy, stem cell therapy, and novel pharmacological agents that target specific pathways involved in nerve degeneration and regeneration. However, more clinical trials and long-term studies are needed to establish their effectiveness.

Combination therapies that target multiple aspects of DPN's pathophysiology—such as metabolic disturbances, oxidative stress, and nerve regeneration—are also being explored. The aim is to provide a comprehensive treatment approach that addresses the underlying causes of DPN, rather than just alleviating symptoms.

4. Discussion

Diabetic Peripheral Neuropathy (DPN) stands out as one of the most difficult microvascular complications of diabetes mellitus (DM) due to its high morbidity and limited treatment options. The condition's pathophysiology is inherently complex and involves a combination of metabolic imbalances, chronic inflammation, and vascular irregularities. While Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) share some overlapping mechanisms in contributing to nerve damage, certain subtle differences remain insufficiently explored. Key contributors to DPN include persistent hyperglycemia, dyslipidemia, insulin resistance, and long-term inflammation, all of which synergistically induce oxidative stress and lead to nerve deterioration.

A critical challenge in DPN research is pinpointing the specific molecular pathways responsible for nerve cell damage. While the polyol pathway, advanced glycation end-products (AGEs), protein kinase C (PKC), and hexosamine pathways have been widely studied for their roles in oxidative stress and neurovascular injury, their interplay remains insufficiently understood. For example, the potential interaction between the polyol and PKC pathways and their combined impact on oxidative damage and vascular complications necessitate further investigation. Emerging pathways, such as Wnt/β-catenin, MAPK, mTOR, and TSH, are now gaining recognition for their influence on the metabolic and inflammatory factors affecting nerve health.

Although substantial progress has been made in understanding DPN, significant knowledge gaps persist. Many of these pathways exhibit dual effects, contributing

to both nerve degeneration and regeneration, making targeted therapeutic interventions particularly challenging. The development of treatments that selectively enhance nerve repair while mitigating damage is crucial. Moreover, it is unclear whether the mechanisms of DPN vary significantly between T1DM and T2DM or share a common foundation. Emerging evidence indicates that therapeutic strategies may need to be tailored to the diabetes subtype, but the molecular distinctions remain to be fully elucidated.

To advance DPN management, researchers must delve deeper into the molecular intricacies of these pathways. Combining pharmacological treatments with non-pharmacological strategies may provide a more effective approach, targeting not just symptoms but also the root causes of the condition. As research progresses, the goal remains to improve the quality of life for individuals suffering from DPN while minimizing the burden of this prevalent complication.

Conclusion

Diabetic peripheral neuropathy is a multifactorial condition with complex pathophysiological mechanisms that involve a combination of metabolic abnormalities, inflammation, and vascular dysfunction. While the current understanding of DPN has advanced, significant gaps remain in elucidating the precise molecular pathways that underlie nerve damage. The interaction between different pathogenic pathways, such as the polyol, PKC, and AGE pathways, as well as newer pathways like Wnt/β-catenin, MAPK, and mTOR, are key areas that warrant further investigation.

The diagnosis of DPN has become more accurate with the use of various clinical evaluation tools and non-invasive tests, such as quantitative sensory testing (QST). However, more sophisticated diagnostic methods, such as nerve conduction studies (NCS) and skin biopsies, may be required in cases with nuanced symptoms or comorbidities. Moving forward, the development of targeted therapies that address the specific molecular mechanisms responsible for nerve damage in DPN remains a critical research priority. Given the complexity of DPN, a combination of pharmacological and non-pharmacological treatments may offer the most effective approach, and ongoing research into combination therapies and individualized treatments will be key to improving patient outcomes.

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Conflict of Interest

The authors declare to have no conflict of interest.

Informed Consent and Ethical Statement

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