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Emerging Viewpoints on Diabetic Neuropathy

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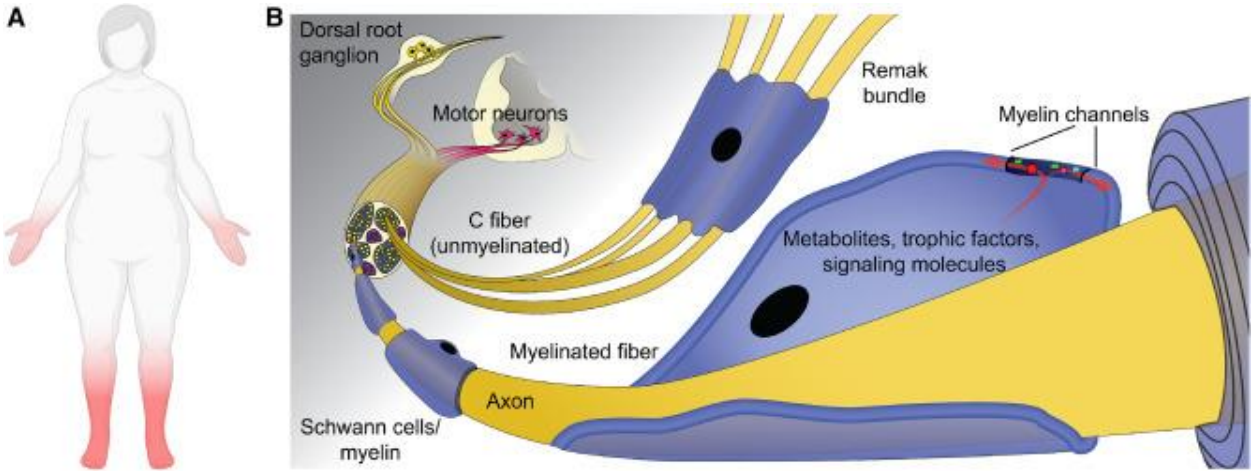
Abstract. The prevalence of diabetes continues to rise, particularly in aging populations. Type 2 diabetes (T2D), which accounts for the majority of cases, is a metabolically acquired condition. Diabetic peripheral neuropathy (DPN), the most common microvascular complication of diabetes, involves length-dependent damage to peripheral nerves. While the pathogenesis of DPN is complex, it can fundamentally be seen as a failure in nerve metabolism and bioenergetics, compounded by the unique anatomy of peripheral nerves—long axons supported by glial cells. This anatomical structure, along with the nerve damage caused by T2D, explains the characteristic distal-to-proximal pattern of DPN symptoms. Early research primarily focused on the role of hyperglycemia in nerve injury and bioenergetic dysfunction, but more recent studies also highlight the contributions of obesity and dyslipidemia. This review will explore peripheral nerve structure, bioenergetics, and the interactions between glial cells and axons, providing a foundation for understanding how hyperglycemia and dyslipidemia lead to bioenergetic failure in DPN. The review will also discuss the lack of disease-modifying therapies for DPN, with a focus on emerging mechanism-based approaches.

Keywords: bioenergetics, diabetes, dyslipidemia, hyperglycemia, metabolic syndrome, mitochondria, obesity, pathophysiology, peripheral neuropathy, prediabetes

The global prevalence of diabetes is steadily increasing, particularly as the population ages. According to the most recent data from 2021, approximately 536.6 million people worldwide are affected by diabetes, representing a 10.5% prevalence rate. This is an increase from 463 million (9.3%) in 2019. Furthermore, projections for 2045 have been revised upwards, with estimates now forecasting 783.2 million cases (12.2%) compared to the previous 2019 projection of 700 million (10.9%). Type 2 diabetes (T2D), which accounts for around 95% of diabetes cases, is primarily caused by lifestyle factors such as poor diet, lack of physical activity, and genetic predispositions. As the body's cells become resistant to insulin, blood sugar levels rise, contributing to obesity and dyslipidemia, which are commonly seen alongside T2D. T2D develops over time, with prediabetes—characterized by insulin resistance and elevated fasting blood glucose (FBG)—serving as a precursor to full-blown diabetes. In contrast, Type 1 diabetes (T1D) results from an autoimmune attack on insulin-producing beta cells, leading to high blood sugar levels (1).

In addition to the challenges of managing diabetes itself, both T1D and T2D patients are at risk of developing secondary complications, the most common of which is diabetic peripheral neuropathy (DPN). DPN is a progressive nerve damage condition that begins in the feet and moves up toward the hands. It can cause pain, loss of sensation, frequent falls, and an increased risk of foot ulcers and lower limb

amputations. Though less common, prediabetic individuals can also develop peripheral neuropathy, which tends to worsen once T2D is fully developed.



The development of diabetic peripheral neuropathy (DPN) is complex and involves impaired metabolism and bioenergetic failure in the nerves, similar to the broader metabolic disturbances seen in Type 2 diabetes (T2D), which also affect other metabolically active tissues like muscle and fat. This nerve pathology is influenced by the unique structure of the peripheral nervous system (PNS), which consists of long axons supported by glial cells. The damage caused by T2D results in a typical pattern of symptoms, starting in the feet and progressing upward. While earlier research emphasized the role of hyperglycemia in nerve damage and energy dysfunction, recent studies also point to the significant contribution of obesity and dyslipidemia in driving DPN's progression(2).

This review explores the risk factors and metabolic pathways involved in prediabetic neuropathy and DPN. It first provides an overview of the PNS structure, the normal bioenergetics of nerve function, and the relationship between axons and glial support. It then examines how hyperglycemia and dyslipidemia lead to bioenergetic failure in DPN, contributing to pain and other symptoms (3). Unfortunately, DPN remains a progressive condition with no disease-modifying treatments currently available, and clinical management focuses primarily on pain relief, proper foot care, and fall prevention. The review concludes by discussing potential novel therapeutic targets based on the underlying mechanisms of DPN.

DPN Risk Factors

The primary risk factors for prediabetic neuropathy and DPN in individuals with prediabetes and diabetes are hyperglycemia and related metrics, such as fasting blood glucose (FBG), glycated hemoglobin (HbA1c), and disease duration. While controlling blood sugar can slow DPN progression in patients with Type 1 diabetes (T1D), its impact is more limited in those with T2D, suggesting that other factors contribute to the onset and progression of DPN. In fact, recent research highlights that the metabolic syndrome (MetS) and its components—such as obesity, dyslipidemia, and hypertension—are key contributors to DPN risk, even in patients without fully developed diabetes.

A decade of research now consistently shows that obesity (e.g., waist circumference [WC], body mass index [BMI]), dyslipidemia, and hypertension significantly increase the risk of prediabetic neuropathy and DPN in patients with prediabetes and T2D. Emerging evidence also points to the MetS as a risk factor for DPN in T1D. Overall, these findings suggest that MetS and its individual components—independent of

blood glucose levels—play a major role in damaging the peripheral nervous system and increasing the risk of DPN (4).

While impaired metabolism is recognized as the primary cause of diabetic peripheral neuropathy (DPN), there has been increasing interest in potential genetic factors that may contribute to the condition. These contributions might be linked to specific genes or through a polygenic risk approach. Research on single genes has focused on those related to metabolism, cholesterol transport, mitochondrial function, oxidative stress defense, and vascular health. However, the results of these studies have been inconsistent. The rise of Omics technologies has led to genome-wide association studies (GWAS), which have helped identify potential genetic candidates for DPN. For instance, one study created a polygenic risk score for Type 2 diabetes (T2D), which showed a weak but significant correlation with DPN. Despite these advancements, genome-wide analyses of DPN are still in the early stages, and the full implications for understanding DPN pathophysiology remain unclear (5).

Peripheral Nervous System (PNS) Structure and Function

The PNS includes 31 pairs of spinal nerves and 10 pairs of cranial nerves, with two cranial nerves—optic and olfactory—classified as part of the central nervous system (CNS). Peripheral nerves are made up of neurons (with their cell bodies and axons), glial cells, Schwann cells (SCs), and various vascular and connective tissues. The axons of neurons that extend to the limbs, especially the lower limbs, are notably long, with a high ratio of length to diameter. This unique structure has important implications for how energy is distributed along the axons. The PNS consists of both sensory and motor neurons, which transmit information toward and away from the brain, respectively. In DPN, sensory neurons in the dorsal root ganglia (DRG) are most commonly affected, though recent studies suggest that motor neurons may also play a role in the disease (6).

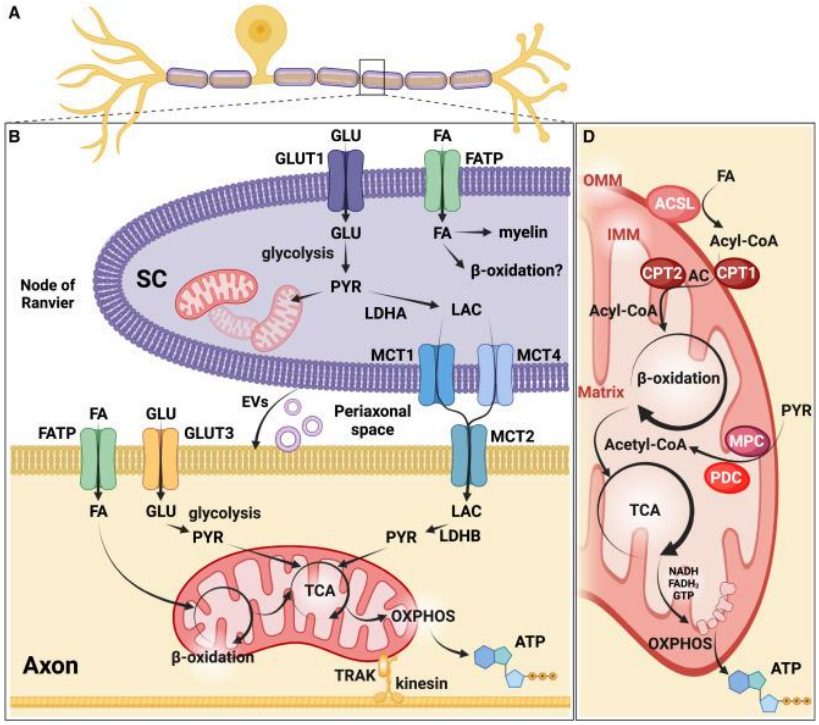
Each sensory axon (or nerve fiber) originates from a DRG neuron and typically conducts electrical impulses. These fibers can be classified into two categories: unmyelinated and myelinated fibers. Unmyelinated fibers, often referred to as small fibers, bundle together into structures called Remak bundles. Myelinated fibers, known as large fibers, are each individually wrapped in layers of myelin produced by Schwann cells. Peripheral nerves usually contain a mixture of both unmyelinated and myelinated fibers. These fibers transmit different types of sensory information at varying speeds: myelinated fibers conduct signals more rapidly through a process known as saltatory conduction, which occurs at the nodes of Ranvier, while unmyelinated fibers conduct more slowly through non-saltatory mechanisms.

In addition to sensory and motor neurons, the PNS also includes autonomic nerves, which regulate involuntary bodily functions, such as organ activity and glandular secretion. Sensory autonomic nerves detect signals like blood oxygen levels and glucose concentration, while motor autonomic nerves control cardiac and smooth muscle, as well as glandular cells. Although this review does not directly address autonomic nerve injury, research suggests that there may be shared mechanisms between DPN and diabetic autonomic neuropathy, which also impacts the autonomic nervous system (7).

Bioenergetics in Healthy Nerve Function

Neurons have a high energy demand to function properly . Even when at rest, axons need energy to maintain a membrane potential, but this demand increases significantly when they fire to transmit signals and release or reabsorb neurotransmitters. This continuous and intense energy requirement makes neurons highly dependent on efficient bioenergetic processes. These processes rely on a steady supply of energy

substrates to both the neuron cell body and the axon, along with tightly regulated metabolism to produce ATP, the cell's energy currency. The delivery of energy substrates to axons is facilitated by substrate transporters, which directly import these molecules into the axons. Additionally, Schwann cells (SCs) contribute to this process through SC-axon metabolic coupling. Once inside the axons, substrate catabolism occurs through cytoplasmic glycolysis and β-oxidation, leading to the production of ATP in the mitochondria.



Energy Substrates and Bioenergetics in Neurons

Glucose and fatty acids (FAs) are the main energy sources that enter cells from the bloodstream. Neurons primarily take up glucose through the insulin-independent glucose transporter 3 (GLUT3) (Figure 2B). Once inside the cell, glucose is first metabolized through glycolysis in the cytoplasm, converting it to pyruvate. Under aerobic conditions, pyruvate is transported into the mitochondria, where it is further broken down in the tricarboxylic acid (TCA) cycle. This process feeds into oxidative phosphorylation (OXPHOS), a process that requires oxygen (Figure 2C). OXPHOS is driven by the mitochondrial membrane potential in the inner mitochondrial membrane and produces a net of 32 ATP molecules per glucose molecule during aerobic conditions. In low oxygen environments, such as during intense neuronal activity, anaerobic glycolysis occurs, converting pyruvate to lactate and yielding only two ATP molecules per glucose molecule (8).

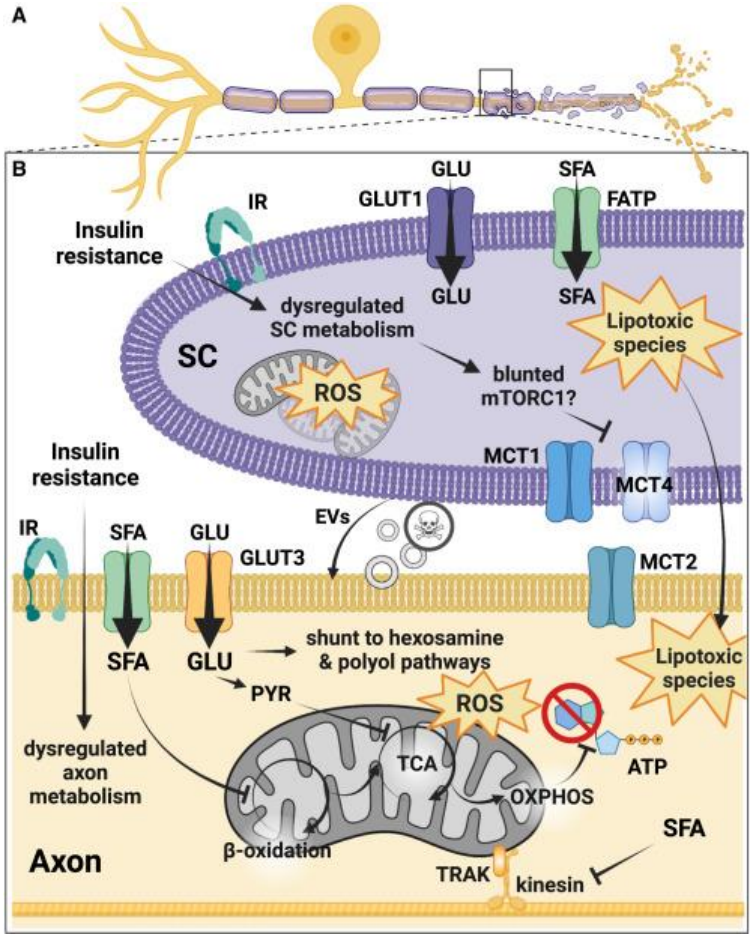
Although neurons primarily rely on glucose for energy, they also have fatty acid (FA) transporters and can use FAs as an energy source. FAs are completely metabolized in the mitochondria. First, an enzyme called acyl-CoA synthetase links the FA to Coenzyme A (CoA), forming fatty acyl-CoA, which is then imported into the mitochondria. Inside the mitochondria, the FA undergoes β-oxidation, breaking it down into acetyl-CoA, which enters the TCA cycle and subsequently participates in OXPHOS (9).

Mitochondria play a critical role in energy production, particularly during periods of high demand, such as rapid firing of neurons. Therefore, neurons rely on tightly regulated mitochondrial dynamics. Mitochondrial biogenesis, or the formation of new mitochondria, mainly occurs in the neuronal cell body. These newly formed mitochondria are then transported along the axon to regions of high energy demand, such as the nodes of Ranvier and synapses. When mitochondria become damaged beyond repair, they are removed through a process called mitophagy. Any disruption in these carefully coordinated processes can cause stress and injury to neurons.

DPN Pathophysiology and Bioenergetic Failure

Diabetes causes damage to both small and large sensory nerve fibers in a distal-to-proximal pattern, leading to the classic "stocking-glove" distribution of sensory impairments . However, diabetic peripheral neuropathy (DPN) can also present as isolated dysfunction of small fibers, where only small fibers are affected. This small fiber dysfunction is primarily caused by damage to the unmyelinated C fibers and thinly myelinated Aδ fibers. The symptoms include pain, such as prickling, burning, or electric shock-like sensations, along with impaired temperature sensation. Small fiber loss is often measured by evaluating intraepidermal nerve fiber density (IENFD) obtained from a skin biopsy, typically taken from the distal leg of patients.

In contrast, large fiber dysfunction involves both demyelination and axonal damage, leading to symptoms like generalized numbness and loss of vibratory and positional sense. This type of dysfunction is often assessed by observing nerve conduction velocities (NCVs), which are typically slowed, and by noting reduced or absent sensory nerve amplitudes, which result from axonal loss. Generally, small fiber dysfunction is believed to occur before large fiber dysfunction in the progression of DPN, although a large recent study has suggested that this may not always be the case. Despite being a progressive condition, the course of DPN is occasionally interrupted by attempts at small fiber regeneration, although this process ultimately fails, leading to further degeneration of the nerves.



Insulin Signaling and Insulin Resistance in DPN

Insulin signaling and the effects of insulin resistance in metabolically active tissues are well-understood. In Type 2 diabetes (T2D), increasing insulin resistance in tissues such as muscle, fat, and liver leads to hyperglycemia and alters lipid metabolism in these organs. Clinical studies have shown that elevated plasma glucose levels, HbA1c, and abnormal lipid profiles are all linked to insulin resistance.

However, much less is known about the role of insulin resistance in peripheral nerves, although both in vitro and ex vivo studies suggest that nerves can develop insulin resistance in T2D. Neurons and Schwann cells (SCs) both have insulin receptors (IRs), and insulin plays several important roles in the peripheral nervous system (PNS), including acting as a neurotrophic factor. While glucose uptake in the PNS occurs through insulin-independent glucose transporters (GLUTs), insulin still influences broader PNS metabolism via nutrient sensors such as the mammalian target of rapamycin complex 1 (mTORC1). These sensors interact with energy regulators like AMP-activated kinase (AMPK) and mitochondrial biogenesis factors such as PGC1α. When insulin resistance develops, it can impair insulin's ability to regulate nutrient and energy responses, disrupting nerve metabolism and contributing to nerve injury .

Therefore, while the central issue in DPN pathophysiology is impaired nerve metabolism and bioenergetic failure due to an overload of energy substrates, there is still limited understanding of how insulin signaling and resistance affect nutrient uptake and utilization in peripheral nerves under both normal and diabetic conditions. Ongoing research is aiming to address these gaps. In the meantime, the following

sections discuss what we currently know about how hyperglycemia and dyslipidemia affect mitochondrial bioenergetics and axonal trafficking. In diabetes, the result appears to be a breakdown in mitochondrial trafficking and bioenergetic failure, particularly at the distal ends of long peripheral axons. This contributes to the characteristic distal-to-proximal nerve damage seen in DPN, which mirrors the pattern of symptoms experienced by patients.

Conclusions

Recent research over the past decade has provided fresh insights into the pathophysiology of diabetic peripheral neuropathy (DPN). While hyperglycemia has traditionally been the primary focus, newer studies have highlighted the role of dyslipidemia in nerve dysfunction. Both hyperglycemia and dyslipidemia contribute to similar disruptions in bioenergetics within the unique anatomical structure of the peripheral nervous system (PNS). Additionally, parallels to the central nervous system (CNS) suggest that Schwann cell (SC)-axon metabolic coupling is essential for nerve health, and this coupling may be impaired in DPN, though more research is needed to fully understand this process.

Future research should further explore the impact of insulin signaling on nerve metabolism in DPN, as well as the potential roles of extracellular vesicles (EVs) and inflammatory mechanisms in disease progression. Computational methods are increasingly being used to uncover the multifactorial and complex nature of DPN pathophysiology. Investigating how hyperglycemia and dyslipidemia influence pain pathways, such as through modulation of ion channels, could reveal promising therapeutic targets. The growing recognition of the combined roles of hyperglycemia and dyslipidemia in DPN is prompting a shift in how potential treatments are viewed. This includes heightened interest in randomized clinical trials exploring dietary changes, medical or surgical weight loss interventions, and exercise as potential treatments for DPN.

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