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# Challenges in Diabetic Micro-Complication Management: Focus on Diabetic Neuropathy

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**Abstract:** The progression of diabetes leads to macro and microvascular complications, including diabetic neuropathy, which is the most prevalent microvascular complication with diabetes. Clinical manifestations of diabetic neuropathy begin with the loss of distal sensory function, pain, and substantial morbidity. It has been evident that ~50% of diabetic patients develop neuropathy at a certain stage in their lifetime. Interestingly, two major subtypes (type I and II) of diabetes do not share the same epidemiology and pathophysiology of diabetic neuropathy; thus, their management or treatment strategies may vary from each other. The past few decades of research suggest that many etiological features, diagnosis, and management complexities depend on the type of diabetes. However, the underlying mechanism of neuropathy in type I and type II diabetes remains unclear. This review provides the current knowledge on successful assessment, management, and pharmacological biomarkers to explore the treatment and surpass current challenges in diabetic neuropathy.

**Keywords:** type I and type II diabetes; microvascular complications; diabetic neuropathy; therapy and challenges

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## 1. Introduction

Diabetes mellitus (DM), a metabolic disease, is currently a major public health issue that greatly affects the socio-economy. The main pathological feature of DM is either insulin secretion discrepancy or pancreatic β-cells damage. The inclination of a sedentary lifestyle has been considered a possible risk factor for the progression of DM. Several chronic and life-threatening micro and macrovascular complications, such as coronary heart disease, cardiopathy, cerebrovascular and peripheral artery disease, nephropathy, retinopathy, and neuropathy, may occur due to chronic metabolic syndrome.

Pain caused by a lesion or disease of the somatosensory nervous system is called neuropathic pain. The most prevalent and frequently observed subtype of this peripheral neuropathy is diabetic neuropathy, which is defined as "pain as a direct consequence of abnormalities in the peripheral somatosensory system in patient with diabetes" [1]. In comparison to other micro-complications (such as retinopathy, nephropathy, and ischemic heart disease), diabetic neuropathy is the most prevalent and their affection rates vary based on diabetes type. Many epidemiologic studies showed that individuals with type II diabetes mellitus (T2DM) are more prone (6.1%) to be affected by neuropathy than individuals with type I diabetes (T1DM) (2.8%) [2–4]. Some other studies also showed that diabetic neuropathy increases dramatically with age and onset of disease. Several reviews [5,6] discussed recent scenarios of diabetes-associated neuropathy, and many of them attempted to provide molecular insight into this secondary complication, while

the molecular mechanism is not fully clear. The prevalence of neuropathy is rising, and the management of neuropathic pain also remains challenging. This review discusses epidemiology, risk factors, management, and pharmacological intervention of neuropathy in diabetic patients.

## 2. Materials and Methods

We used PubMed and Google Scholar to search data for this review; we searched through these databases using the keywords 'Secondary complications', 'Microvascular complications', 'Neuropathy prevalence and epidemiology', and 'Risk factors and management of neuropathy' in diabetes. Our database searching began on 21 January and ended on 21 March. Over 500 papers were found interesting, and later we conducted a primary screening for further analysis and inclusion in the review. Finally, we selected 70 articles to critically analyze, and we summarized their findings in the current review. Other than the keywords, we followed specific time limit data for inclusion or exclusion in this study; we included data from the past 5–10 years and excluded data beyond this time limit. However, for the epidemiological studies, we did not adhere to time constraints, as these studies are mostly long-term cohort analyses, so constrain within a specific timeframe might lower their findings' significance.

## 3. Epidemiology of Neuropathy

Diabetic neuropathy is the most common microvascular complication that has a major impact on patients' quality of life [7]. Each study used a distinct definition of neuropathy; together with this, the prevalence and occurrence of neuropathy have been assessed several times. A study using two population-based screenings has reported 1–4% of neuropathy prevalence, in which 40–55% cases were secondary to diabetes [8,9]. Another similar study [10] reported ~50% neuropathy as a secondary complication to diabetes after diagnostic workup by a neurologist. However, a cohort study on the people of the Netherlands revealed that neuropathy incidence changes dramatically with age [11]. Recent studies showed an increase from <50 to ~300 per 100,000 person-years in individuals of <50 years and >75 years of age, respectively, where 32% of total cases were found in diabetic patients.

In addition, the incidence and prevalence of diabetic neuropathy varies according to T1DM or T2DM occurrence. Epidemiological studies confined that the incidence of neuropathy is higher in individuals with T2DM (6.1% person-years) than in T1DM (2.8% person-years) [2,3,12]; while the prevalence of neuropathy is similar in both T2DM and T1DM, 8–51% [13,14] and 11–50% [14–16], respectively. The neuropathy incidence rate is higher in T2DM; however, the prevalence rate is similar to T1DM, which could be due to the multiple secondary factors, but the most crucial factor could be the age of onset of diabetes. Indeed, the duration of the disease has potential influences on neuropathy prevalence. A follow-up study, after 10 years, of diabetic patients (86 patients and 121 control subjects) reported an increase from 8% to 42% in cases [17]. Another cohort study (2368 patients; $HbA1_c \leq 13.0\%$ and no class III or IV heart failure) confirmed 50% diabetic neuropathy in patients with advanced T2DM and coronary artery diseases (CAD) [3]. A 4-year follow-up study also confirmed 66–72% of neuropathy incidences in those who had no neuropathy at the baseline [3]. These data suggest that neuropathy is common in diabetic patients and gives paramount importance to fortifying diagnostic, screening, and preventive strategies.

## 4. Risk Factors of Diabetic Neuropathy

Diabetic patients often suffer from secondary complications of large and small blood vessels in damage-induced system failure in an advanced stage of the disease termed as macrovascular and microvascular system complications. However, diabetic morbidity is mostly reported due to macrovascular complications, such as coronary and cerebrovascular diseases [18], but the microvascular network in the kidney, eyes, and nerves are more common [19] and also has a substantial effect on mortality [18].

Diabetes is one of the major causes of nerve damage, especially in the longer peripheral nerves, leading to lower limb denervation [20]. There are several sub-classes of diabetic neuropathy, and the most common forms are distal symmetric polyneuropathy (or peripheral neuropathy), autonomic neuropathy, atypical neuropathy, and non-diabetic neuropathy [2,21]. Aside from the normal manifestations of increased pain and decreased quality of life in diabetic neuropathy, 15–20% of diabetic persons are at risk of foot ulceration and a 15-fold risk of lower limb amputation when compared to non-diabetic individuals [21–23]. Interestingly, almost 50% of individuals with diabetes developing lifetime risk diabetic neuropathy [24,25]; it is one of the least studied diabetic complications due to its direct and accurate measurement difficulty. Therefore, treatments rely on glucose control, symptomatic therapy, and pain management.

### *4.1. Neuropathy Risk Factors*

Diabetic neuropathy is a multifactorial condition that includes several risk factors, such as hemoglobin $A_{1c}$ (HbA1c) level (a measurement of glycated hemoglobin to determine average daily glucose level), hypertension, smoking, and obesity [16]. The co-occurrence of neuropathy and glucose intolerance in diabetic patients has provided an important insight into glucose dysmetabolism in developing neuropathy and hyperglycemia. The early sign of neuropathy progression is the involvement of small-nerve-fibers [26]. Both human and animal models of diabetes showed aggregation of polyols during the progression of neuropathy, but the role of accumulated polyols is not clear yet. Several aldose-reductase inhibitors have also failed to ameliorate diabetic polyneuropathy [27], suggesting an unclear role of aggregated polyols.

Some studies also suggested that mitochondria of sensory neurons at the dorsal root ganglia might have a potential role in diabetic neuropathy [28]. In accord, mitochondria of hyperglycemic neurons are the source of mass production of reactive oxygen species (ROS), which could damage DNA and membranes and lead to nerve desensitization. Impairment in mitochondrial fission-fusion homeostasis regulates mitochondrial shaping and number and could dysregulate cellular functioning and lead to degeneration [29]. The mass production of oxidative stress has been suggested as a major culprit of diabetic neuropathy [28]. Potential antioxidants that could scavenge hydroxyl, superoxide, and peroxyl radicals, such as α-lipoic-acid, proanthocyanidins, luteolin, rutin, and quercetin, have been shown to improve nerve conduction velocity and symptomatic relief in diabetic neuropathy [28,30]. Moreover, advanced glycation end products (AGE) from hyperglycemia increases cytokines production in monocytes and endothelial cells. It has been speculated that AGE might injure nerve fibers by affecting matrix metalloproteinases [31].

### *4.2. Genetic Risk Factors of Neuropathy*

An early familial clustering analysis showed a history of diabetic neuropathy in a family increased 2.2-fold lifetime risk of developing diabetic neuropathy [32]. Genome-wide associated studies (GWAS) reported, respectively, 11–15% [33,34] and 6% [35] risk of the single nucleotide polymorphism (SNP) heritability of diabetic neuropathic pain and foot ulcers. Recently, three different studies on the same Scottish population with diabetic neuropathy reported several SNPs associated with diabetic nerve pain and foot ulcers. Two groups have conducted primary GWAS and found three distinct signals are associated with diabetic nerve pain [21,33,34]. They found SNP rs71647933 at ZSCAN20 in the female case analyses and SNP rs6986153 at chr8q23 in the male case analyses, while sex-combined analyses only reported SNP rs71647933 in ZSCAN20 and SNP rs17428041 in one mRNA transcript of DOK2 [21,33,34]. A third group conducted a GWAS investigation on foot ulcers in diabetic neuropathy [35]. This group found that intronic SNP rs80028505 in MAPK14 is associated with foot ulcers compared to their cases and controls with diabetic neuropathy [21,35]. Although these studies found potential genomic links, their single cohort includes <1000 cases and no replication. Another study on European ancestry individuals found that SNP rs13417783 at chr2q24 has a significant protective effect for

T2DM-associated peripheral neuropathy [36]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) conducted clinical trial reached significance with SNP rs13417783 inclusion in diabetic retinopathy, triglyceride levels, and eGFR (also associated with some other micro- and macro-vascular complications, but not significantly) [37].

### *4.3. Other Risk Factors*

Patients suffering from distal sensory polyneuropathy often possess etiologies other than diabetes itself [38,39]. A study of patients with symptomatic neuropathy reported diabetes causes neuropathies in 74% of the group [38]. One-third of patients were diagnosed with neuropathy not related to diabetes. A major portion of these patients had chronic inflammatory demyelinating neuropathy that caused non-diabetic neuropathy. Diabetes is one major cause of polyneuropathy, but not the only one. Several other general factors, such as alcoholism, vitamin deficiency, drug-induced neuropathy, monoclonal gammopathy, POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) syndrome, and amyloid polyneuropathy, have also been attributed to neuropathy pathogenesis. Therefore, these factors also need a diagnosis to find the exact cause, which would help in designing proper treatment plans.

## 5. Mechanisms of Diabetic Neuropathy and Associated Pain

### *5.1. Mechanisms of Diabetic Neuropathy*

Diabetic neuropathy is a unique neurodegenerative disorder that impairs the peripheral nervous system. Although it is still under research, primarily diabetic neuropathy targets sensory axons, autonomic axons, and motor axons. Progressive neuropathies retract terminal sensory axons in the periphery. Neuropathic damages begin with distal sensory first, such as loss of distal leg epidermal axons and damages to the proximal limbs sensory system. In addition, diabetic neuropathy could target entire neurons. Again, it is debated that from where it starts. Whether the peripheral axons and associated Schwann cells are the primary targets or neuronal cell bodies at dorsal root ganglia remains unclear.

Primarily diabetic neuropathy does not demyelinate. In progressive conditions, chronic hyperglycemia severely affects Schwann cells and causes demyelination [40,41]. Schwan cells provide mutual support to axons; damage in Schwann cells might cause damage to the axon, which might change a proteins' position at the Ranvier node and axon trafficking [42]. Injuries to Schwann cells might also cause inadequate support to the cytoskeleton of axons and improper intra-axonal mRNA translation within the distal axon [43].

The changes in neuronal cell bodies also affect axons, especially distal terminals. Chronic diabetes changes sensory neurons phenotype at the dorsal root ganglia, which links their relationship with the distal axon branches. A rat model of chronic T1DM showed a gradual loss of neurofilaments synthesis and export [44]. These neurofilaments are structural scaffolds of the axon. Another preclinical study in diabetic animals proposed endoplasmic reticulum stress in diabetes could potentiate peripheral nerve damage and affect functioning [45]. Although the exact mechanism of the disease pathogenesis is not clear yet, several in vitro and in vivo models of diabetes have shown hyperglycemia could alter several critical functions in plasticity, including growth-associated protein 43 (GAP43), Heat Shock Protein (HSPs) expression [46,47], and poly(ADP-ribose) polymerase (PARP) [48,49] at the dorsal root ganglia region (Figure 1). These data indicate that dysfunction in these pathways promotes abnormal protein processing, inducing oxidative damage and mitochondrial dysfunction, which, in turn, may damage peripheral nerves [43].

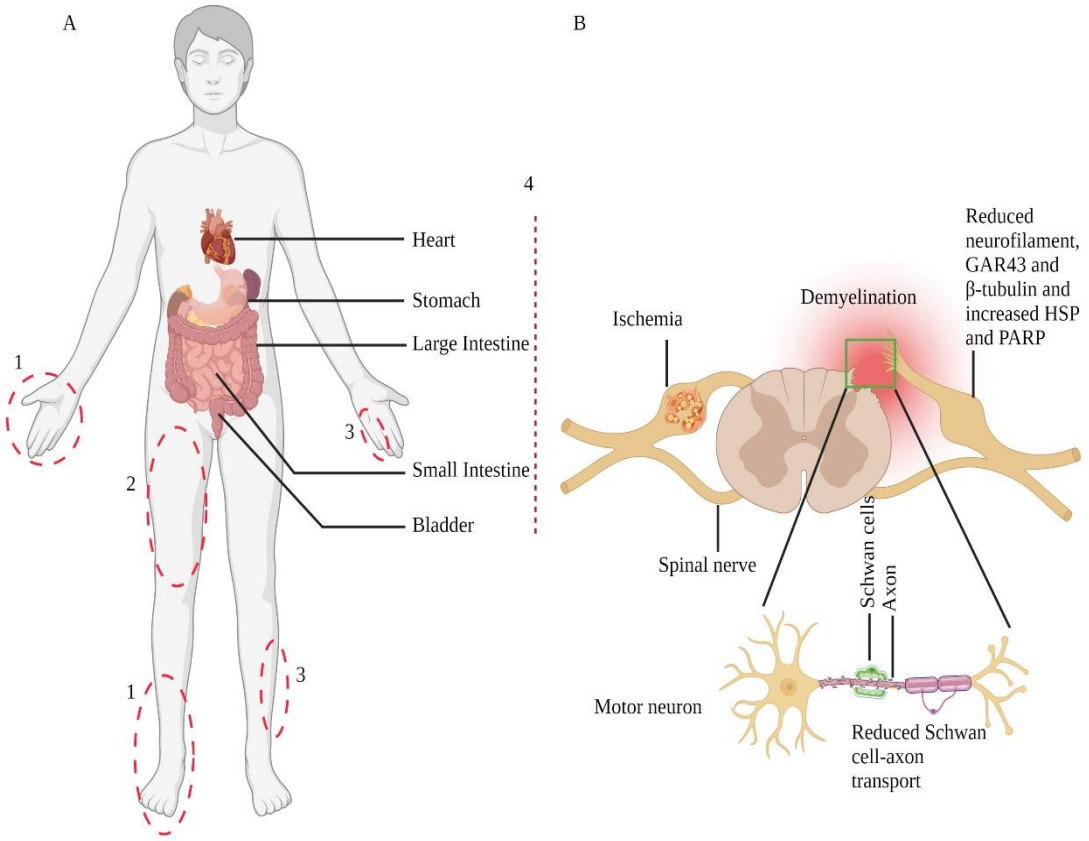


**Figure 1.** Nerve injury-prone areas and alteration of the peripheral nervous system in diabetic neuropathy. Diabetic neuropathy primarily affects distal sensory systems (1), eventually causing radiculopathy (2), mononeuropathy (3), and autonomic neuropathy or treatment-induced neuropathy (4) (part **A**). Sensory neurons transmit their terminal information from the periphery to the dorsal horn of the spinal cord (part **B**); contrarily, spinal cord-residing motor neurons relay information to the periphery. The Schwan cells myelinate axons and play a crucial role in preserving axonal functions. Therefore, in response to cellular injuries, such as diabetes, damaged Schwan cells or axons lead to neuronal cell body damage. These changes also include Schwan cell-axon transport, change in protein expression, demyelination, and degeneration. Adopted from REF [50].

### *5.2. Hyperglycemia in Neuropathy*

The peripheral nervous system plays a critical role in energy substrates synthesis and their uses during diabetic neuropathy. The understanding of this mechanism might give a clear picture of the pathophysiologies of diabetic neuropathy. Each Schwann cell, dorsal root ganglia, and axon produces NADH and $FADH_2$ from glucose and fatty acids, and Schwann cells uptake long-chain fatty acids to convert them into one molecule of acetyl-CoA via β-oxidation. Afterward, it transports this acetyl-CoA to the tricarboxylic acid cycle to produce NADH and $FADH_2$. When the transport system is saturated in diabetes, due to the overload of glucose substrate, the acetyl-CoA is converted into acylcarnitines. Accumulation of these acylcarnitines is pathogenic for both Schwann cells and dorsal root ganglia neurons, leading to axonal degeneration and diabetic neuropathy [51].

On the other hand, transportation of NADH and $FADH_2$ into mitochondria yields ATP via oxidative phosphorylation, which also produces ROS as a byproduct. In normal physiology, bodies innate antioxidants, such as superoxide dismutase, glutathione, and catalase, neutralizes ROS [52,53], while the glucose substrate is overloaded, oxidative phosphorylation occurs more frequently and produces more ROS in diabetes. These events lead to mitochondrial dysfunction and cause metabolic and oxidative damage to Schwann cells and dorsal root ganglia neurons [54,55]. Glucose overload also forces the glucose metabolism via polyol and hexosamine pathways, which increases ROS and inflammatory

cytokines release and leads to mitochondrial damage [43]. Malfunctioned mitochondria lose their normal energy production capacity, eventually promoting axonal disruption and degeneration [56].

### *5.3. Malfunctioned Insulin Signalling in Neuropathy*

Some preliminary research strongly suggests that insulin and nerve growth factor (NGF) have structural similarities. Insulin actions on neurons [57] or insulin increased substantial neurite outgrowth cultured adult sensory neuronal cells [58]. Insulin receptors are also expressed in dorsal root ganglia neurons and axons [59,60], while the expression substantially declines in experimental diabetic neuropathy. The intrathecal or intranasal delivery of insulin, independent of glucose levels, has shown reversal of diabetic neuropathy-induced decline [59,61]. Insulin administration near the nerve or in the plantar skin, where it accesses dermal axons, also repairs abnormalities of diabetes in experimental animal models [62,63]. Although these findings are promising, the reversal of hyperglycemia by insulin has little effect on neuropathy with T2DM. In contrast, normoglycemia by insulin therapy has substantial benefits in T1DM and neuropathy. The major obstacle of neuropathy treatment via insulin in T2DM is insulin resistance. Phosphorylation of insulin-receptor substrate 2, which is a downstream mediator of the insulin signal transduction pathway, might have an important role in insulin resistance [64].

## 6. Diagnosis and Management of Neuropathic Pain

### *6.1. Assessment of Pain*

Neuropathic pain is a group of syndromes with different pathophysiology and clinical manifestations. It is of the utmost importance to assess the source of pain that confirms the underlying disease in the peripheral or central nervous system. Although the basic diagnosis system is the same for both peripheral and central nervous system neuropathy [65,66], their assessment tools are different, such as punch skin biopsy for peripheral while magnetic resonance imaging for central neuropathy [67]. According to the guideline of the Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain (IASP), the first step in neuropathic pain diagnosis is assuring whether the pain is neuropathic or if the patient has a neuropathic component in mixed pain syndromes [65,66]. The stepwise approach for diagnosing and managing neuropathic pain contains the history of the patient, physical examination, and confirmatory tests. The NeuPSIG has established four distinct steps to grade and determine neuropathic pain [66,67]: Step 1: a medical history of a patient should indicate the patient has a disease that can cause neuropathic pain. Step 2: the underlying disease that can distribute pain. If this condition is met, the physician then performs a detailed clinical examination. Step 3: as the traditional testing tools are incapable of determining the spatial extent of perceived ongoing pain, the spatial extent of sensory signs serves as a surrogate. Once this condition is met, the pain is probably neuropathic pain. Step 4: a suitable confirmatory test performed based on the suspected disease. This method verifies neuropathic pain and aids in the appropriate diagnosis and therapy [66,67]. These steps mostly follow an algorithm of neurological diagnosis, and other available guidelines also agree with this system. The accuracy of determining the 'definite neuropathic pain' by this system depends on the experience and skills of the physician. Although it is a well-accepted diagnosis guideline, the implication is limited because of conventional clinical settings due to test–retest reliability of clinical assessments [68,69]. Lack of confirmation may lead to underdiagnosis of neuropathic pain patients to those in whom neuropathy is the primary or sole symptom [66–68,70,71], resulting in inaccurate treatment.

There are two types of confirmatory tests used in the assessment of neuropathic pain individuals. 1. Confirmatory test of sensory changes, 2. Confirmation of specific underlying disease of the somatosensory nerves that explains the symptom [66,72–74]. Several tests investigate and confirm somatosensory function and changes in the neuropathic event. These tests are further subdivided into the structural (e.g., nerve biopsy, punch skin, corneal

confocal microscopy) and functional (quantitative sensory testing, neuropsychological assessment) categories. These tests are used in research settings and diagnoses of patients with atypical clinical manifestation [27,50]. It is to be noted that not all incidences of neuropathy in patients with DM are associated with diabetes or due to diabetes. Several other diseases could manipulate this concept, such as thyroid, autoimmune and infectious diseases, vitamin deficiencies (specifically vitamin B12 deficiency), and intoxications. To confirm 'definite diabetic neuropathy', a combination of clinical manifestation and proper laboratory assessment tools, as well as the exclusion of these diseases during research settings or diagnosis, should be required [2,67,75,76].

### *6.2. Management*

Current diabetic neuropathy management includes glycemic control, foot care, and symptomatic treatment. Indeed, glycemic control has a benefit/risk ratio in T2DM patients [77,78], but hyperglycemia is not the prime driving cause of all complications in T2DM [27]. If it were the prime cause, any diabetic complications, including neuropathy, would have been efficiently treated because control for glycemia was first given to all T2DM patients [79]. Although several studies claim that efficient glucose control significantly reduces or delays neuropathy in T1DM [80,81], the effectiveness in T2DM has yet to be uncovered [82–85]. It is possible that the pathophysiology of neuropathy differs between T1DM and T2DM [82]; therefore, the treatment strategy needs to be adjusted. A cohort study showed that intensive glucose control at the early phase could avoid diabetic complications and mortality [86]. However, extensive glucose control could lead to hypoglycemic episodes [82] and hypoglycemia-induced neuropathy [87,88]. Since neurons consume more glucose than other cells, hypoglycemia can be devastating; thus, excessive glycemic control should be avoided.

Diabetic neuropathy is the primary risk factor for foot ulcers. In this condition, patients are suggested to reduce plantar pressure during orthoses and wear soft footwear and partake in regular skin, nail, and ulcer care [89].

In addition, all neuropathic pain is not due to diabetic neuropathy, it is challenging to treat neuropathic and diabetic neuropathy pain in general. Three main points consider treating DM-induced neuropathy: management of diabetes, neuropathy, and symptomatic treatment of pain. Different organizations have suggested several guidelines to manage diabetic neuropathy-related pain [67]. With their consent, the following three phases of pharmacological intervention may be useful: Step 1: first-line therapy of tricyclic antidepressants (e.g., amitriptyline), serotonin-norepinephrine reuptake inhibitors (e.g., duloxetine), gabapentin, and pregabalin. Step 2: the second line of treatment could include tramadol (a weak opioid and SNRI), and Step 3: the last line of treatment commonly includes potent opioids, anti-convulsants, and cannabinoids.

## 7. Pharmacological Targets and Future Perspective

Pharmacological treatment strategies to treat diabetic neuropathy include central and peripheral nervous system excitability reduction. The different ion channel modulators (e.g., lidocaine and capsaicin), synaptic transmission modulators (e.g., gabapentinoids), tricyclic antidepressants, duloxetine, and opioids are used for this therapy. However, theoretical effectiveness has yet to be achieved in actual clinical trials.

Since Nav1.7 channel inhibition showed insensitivity to pain in patients [90], a specific Nav1.7 inhibitor could deliver potential therapeutic efficiency. Several designated Nav1.7 inhibitors have been tested, but none of them successfully reached the clinical trial. Lack of targeting selectively Nav1.7 is the most common challenge. Even though there are the most compelling therapeutic targets it is difficult to find a specific ligand agonist or antagonist. Lacosamide showed efficacy in diabetic neuropathy by inhibitory action on Nav1.7, but there is no clinical trial that supports its efficacy [91,92].

Neuroinflammation might be considered a therapeutic target. Immune cells and glia play an essential part in the development of neuropathy. Most of the compounds that can

inactivate or disrupt glial function and attenuate pain in animal models of neuropathy have failed to reproduce their effect in humans—for example, minocycline, a commonly used second-generation tetracycline antibiotic and nonspecific blocker of microglial activation. Minocycline has shown potential effects in the preclinical model but was not clearly demonstrated in the clinical trials [93–96]. One of the most reliable first-line T2DM therapies, Metformin can reduce microglial activation in the spinal cord and block neuropathic hypersensitivity. However, its effect is specific to sex; metformin-induced microglial inactivation has been seen in male mice, where the drug treatment worsens the situation in female mice [97]. The role of sex differences in the microglia-mediated neuropathy mechanisms could explain several questions and propel this treatment target. Although the clinical translation of the inflammatory and metabolic functions alteration model is challenging, glycemic control and improved lifestyle remain the only disease-modifying therapy for diabetic neuropathy. The evidence frequently indicates that neuropathy requires multiple intracellular signaling pathways [98] and suggests that old targets might be significant for new pharmaceuticals [91,92,98].

Moreover, several biomarkers could be targeted to intervein progressive inflammation and nerve damages. Toll-like receptors (TLR), an innate immune receptor family, have been found related to neuropathy. TLR2/4-knockout mice model did not develop neuropathy after high-fat feeding [99]. Further, TLR4 regulates cytokines, such as TNF-$\alpha$ and IL-6 production. Assessing human peripheral blood mononuclear cells from T2DM patients with neuropathy revealed an increase in TNF-$\alpha$ and IL-6 levels, clarifying the role of TLRs in neuropathy pathophysiology [100]. Furthermore, adiponectin, a 30 kDa protein secreted from adipocytes that regulate lipid and glucose metabolism and insulin sensitivity, has been suggested to increase during neuropathy progression [101–103]. Although the anomalous expression of NGF [104,105] and HSP27 [106] in diabetic neuropathy patient's serum has been reported by several studies, their exact role in neuropathy pathogenesis is under debate. However, the exogenous NGF treatment or HSP27 targeted therapy may protect from neuronal loss in diabetic neuropathy, additional research is required to understand their role in disease.

## 8. Conclusions

Recent scientific advances have increased the awareness of diabetic neuropathy; however, progress has been slower than required to meet the impending healthcare crisis. Large-scale preclinical and clinical studies may alter treatment parameters for diabetic neuropathy. In addition, diabetes and obesity are increasing at an alarming rate; therefore, preventative, and therapeutic intervention for diabetic neuropathy is essential. Unfortunately, current knowledge on diabetic neuropathy is still at the primary level, which may prevent pharmaceuticals from conducting large-scale research and clinical trials, leaving this illness with microvascular complications and causes a high mortality rate.

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