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REVIEW ARTICLE

Insight on development and management of neuropathic pain

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ABSTRACT

Diabetic peripheral neuropathy (DPN) impacts up to 50% of diabetic people and is a major cause of illness and death. Its neuropathic symptoms, which can be painful, and insensitivity increase the risk of burns, injuries, and foot ulcers. Several recent studies have identified several risk factors for developing DPN, including obesity, poor glycemic control, diabetes duration, hyperlipidemia, impaired insulin signaling, and lipid oxidation and inflammation. Inspection of the lower limbs is necessary for the diagnosis. Anticonvulsant or tricyclic medications, which are typically used, may be needed. Peripheral neuropathy patients should be treated by a podiatrist and given preventative education since they risk developing insensate foot ulcers. A multidisciplinary approach to preventing and managing foot problems, promptly diagnosing and treating neuropathic pain, and controlling specific cardiometabolic objectives should all be included in treating patients with DPN. The concept of categorizing patients based on different aspects of their pain to enhance analgesic response is being researched, and new drugs are being developed to manage painful DPN.

KEY WORDS: Cardiometabolic, Hyperglycemia, Hyperlipidemia, Paresthesia, Sensorimotor polyneuropathy

INTRODUCTION

Diabetic peripheral neuropathy (DPN) is the most frequent neuropathic condition among people with diabetes. In a new definition, the Toronto Consensus Panel on Diabetic Neuropathy described DPN as a "symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure and cardiovascular risk covariates."[1] DPN begins in the toes and progresses proximally; once established in the lower limbs, it affects the upper limbs, with sensory loss following the typical "glove and stocking" distribution pattern. Painful symptoms such as burning, tingling ("pins and needles" or paresthesia), shooting (like electric shock), or lancing (stabbing) are present in approximately one-third of DPN patients and approximately 20% of all diabetic patients.[2] DPN can take numerous forms. Distal symmetric polyneuropathy is the most frequent, accounting for roughly 75% of all diabetic neuropathies. It can be characterized as mostly small-fiber, large-fiber, or mixed small and large fibers.[3] Mononeuropathies (mononeuritis multiplex), (poly) radiculopathies, and treatment-induced neuropathies are examples of atypical DPN. Diabetes is closely connected with mononeuropathies, which typically damage the median, ulnar, radial, or common peroneal nerves.[4] Cranial nerve involvement is uncommon and typically manifests as an acute mononeuropathy involving cranial nerves III, IV, VI, or VII. Unilateral thigh discomfort, weight loss, and motor weakness are classic symptoms of diabetic radiculopathy, typically affecting the lumbosacral plexus.[5] After periods of acute metabolic dysregulation (such as ketoacidosis) or after a sudden and radical change in glycemic control (such as insulin neuritis), treatment-induced neuropathy can arise as a rare iatrogenic

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occurrence. Each atypical form of DPN responds well to a combination of supportive care, medication management, and physical therapy and typically resolves on its own within a few months.[6]

Although the mechanism of DPN is unknown, chronic hyperglycemia plays an important role in its pathogenesis. Hyperglycemia causes irregularities in the nerve polyol, hexosamine, and protein kinase C (PKC) pathways through numerous metabolic changes.[7] These changes cause the release of proinflammatory cytokines, the accumulation of advanced glycation end products, and the production of reactive oxygen species. Concurrently, microangiopathic alterations in the vasa nervorum cause neuroischemia.[8] These alterations are worsened further by dysfunctional endothelial nitric oxide-mediated vasodilatory processes (nitrosative stress). These glucotoxic metabolic and ischemic alterations cause DPN by causing nervous system oxidative stress, apoptosis of both neurons, and supporting glia.[9] Although DPN worsened substantially in both treatment groups, in the Epidemiology of Diabetic Complications study, an observational follow-up of participants, its prevalence and incidence remained significantly lower in the previously intensively treated group 14 years after the end of the trial.[10]

New therapeutic approaches need to be evaluated to reduce neuropathic symptoms and improve outcomes for people with DPN because of the complications associated with the condition, such as paresthesia, sensibility loss, ulcers, osteomyelitis, deformities, gangrene, and ultimately foot amputation.[11] Some research suggests that maintaining blood sugar levels at or near normal is the best strategy for avoiding or delaying DPN. In contrast, other research suggests that even good glycemic control cannot stop or reverse nerve damage. It is impossible to achieve near normoglycemia in all patients with diabetes mellitus, even if this was the optimal preventive measure.[12] People with DPN have been studied using a wide range of pain treatments, including antidepressants, anticonvulsants, topical agents, and opioids; nevertheless, medication adherence is low due to the common side effects.[13]

However, a Cochrane review found that the strongest evidence for the value of intensive glucose control in type 1 diabetes came from studies of younger patients in the early stages of the disease and that the benefits of tight blood glucose control seemed to weaken once complications were already established.[9] Notably, in type 2 diabetes, increasing glycemic management alone does not have the same degree of influence on the incidence of DPN (5–9% relative risk decrease). Even when trials, such as the ACCORD study, have demonstrated that tighter glucose control may be beneficial in preventing the progression of DPN in type 2 diabetes, confusion has arisen when it has been reported that a self-reported history of DPN at baseline is associated with an increased risk of mortality with intensive glycemic treatment.[14] However, neither the Michigan Neuropathy Screening Instrument documented DPN nor amputation history was linked to a distinct impact on mortality across the two therapy groups in this investigation. This mismatch shows that different approaches to DPN detection may identify distinct populations and call for additional research. In the DIAD study, it was also clear that different DPN indices varied widely in how well they could predict outcomes. Multifactorial cardiovascular risk therapies have not slowed the development or decreased the prevalence of DPN in several other long-term investigations involving patients with type-2 diabetes or pre-diabetes. DPN should be stressed as not being a primary endpoint in these studies, and its inclusion seemed to have been a last-minute decision given the use of sporadic and insensitive techniques to detect and monitor DPN.[15,16]

DPN was linked to glycemic control and disease duration, according to the EURODIAB IDDM Complications Study, which included 3250 patients with type 1 diabetes from 31 sites in 16 different European countries. After data were adjusted for diabetes duration, the prevalence ranged from 17 to 41%, with lower glycosylated hemoglobin (HbA1c) levels associated with lower prevalence rates and higher levels associated with higher prevalence rates, even though the 28% baseline prevalence of DPN was significantly related to HbA1c. Even individuals with adequate glycemic control (HbA1c<5.4%, similar to Diabetes Control and Complications Trial HbA1c of 7%), however, nevertheless, acquired microvascular damage, indicating that variables other than glycemic control and illness duration are implicated.[17] Follow-up information from the type 1 diabetic EURODIAB cohort of patients showed that, after 7 years, over one-fourth of type 1 diabetic patients acquired DPN, with age, duration of diabetes, and poor glycaemic control being the main contributors. In addition, potentially modifiable cardiovascular risk factors such as obesity, smoking, hypertension, and hyperlipidemia were linked to the development of DPN.[18,19]

RISK FACTORS OF DPN

It has been proposed that oxidative stress and inflammation cause nerve damage and cell death, eventually resulting in DPN. Hyperglycemia, dyslipidemia, and insulin resistance are all caused by the dysregulation of metabolic pathways, which lead to an imbalance in the mitochondrial redox state. This leads to more reactive oxygen species in the mitochondria and cytosol.[20] This causes the loss of energy stores in the axons and damage to the axons, which leads to peripheral neuropathy [Figure 1 a-c]. The first changes in DPN happen in the unmyelinated C fibers. These changes cause pain, allodynia, and hyperesthesia. When demyelination is stronger than remyelination, segmental axonal demyelination and axonal degradation of myelinated fibers happen. These changes cause a loss of feeling in the

extremities that worsen from the extremity to the nerve. This is called DPN.[21]

Dyslipidemia

People with type 2 diabetes are more likely to have dyslipidemia. Dyslipidemia is linked to diabetic neuropathy, and researchers have found several reasons. *In vitro*, tests have shown that free fatty acids directly damage Schwann cells.[22] They also have systemic effects, such as making adipocytes and macrophages release more inflammatory cytokines. Plasma lipoproteins, especially LDLs, can be changed by oxidation or glycation.[23] These changed LDLs can bind to extracellular receptors, such as the oxidized LDL receptor LOX1, toll-like receptor, and RAGE. These set off signaling cascades that activate NADPH oxidase and cause oxidative stress. Furthermore, cholesterol can be broken down into oxysterols, which have been linked to the death of nerves.[24]

Impaired insulin signaling

While insulin does not participate in the transport of glucose into neurons, it has been demonstrated to have neurotrophic effects, increasing neuronal development and survival. It is thought that diabetic neuropathy is caused by a decrease in this neurotrophic signaling due to a lack of insulin (in type 1 diabetes) or insulin resistance (in type 2 diabetes).[25] Insulin insensitivity in neurons is caused by blocking the PI3K/Akt signaling pathway, just like in muscle and fat tissue. If this route is messed up, it can cause mitochondrial dysfunction and oxidative stress, worsening neuropathy.[26]. In people with type 1 diabetes, a drop in C-peptide can cause nerve damage in several ways, including a drop in sodium-potassium ATPase activity, endothelial nitric oxide synthase activity, and endoneurial blood flow. Neuropathy can take longer to get worse in people with type 1 diabetes if they do not take C-peptide.[27]

Lipid metabolism and inflammation

Schwann cell dysfunction has been connected to altered lipid metabolism and subsequent inflammatory effects, both associated with diabetes and changes in lipid levels in the circulation and neurons.[28] Diabetes-related triglyceride, cholesterol, and free fatty acid accumulation in blood plasma contribute to lipid-mediated neuropathology through unknown processes that may involve oxidative and inflammatory pathways in Schwann cells.[29] High-fat diets in rodents result in an accumulation of oxidized lipids and the activation of lipoxygenases in peripheral nerves, both of which are signs of pre-diabetes. In addition, the build-up of oxidized LDLs in peripheral nerves stimulates the development of oxidative stress, which has been linked to reduced nerve conduction velocity and sensory impairments.[30]

Oxidative stress

When there is an imbalance between the generation of reactive oxygen or nitrogen species, respectively, and antioxidant defense, oxidative or nitrosative stress is brought on. In DPN, the formation of reactive oxygen species outweighs the body's natural antioxidant defenses, compromising brain blood flow, nerve conduction, neurotrophic support, and neuronal mitochondrial function.[28] The formation of mitochondrial superoxide caused by hyperglycemia has been proposed as a unifying theory for diabetic microvascular problems. When superoxide is produced excessively through the electron-transport chain, it inhibits the function of the GAPDH enzyme, which diverts upstream glycolytic products into the polyol, hexosamine, PKC, and AGE pathways, which are molecular pathways of glucose overutilization.[31]

MANAGEMENT OF DPN

Glycemic control

According to the Diabetes Controls and Complications Trial, people with type-1 diabetes who maintain strict blood glucose control have a 60% lower risk of developing DPN. The situation with type-2 diabetes is different, as numerous studies have shown that stringent glycemic management has no appreciable effect on patient risk for polyneuropathy.[12] A systemic evaluation conducted by Callaghan *et al*. has shown that glycemic management inhibits the development of polyneuropathy in people with diabetes.[32] Strict control, however, also increased the chance of negative outcomes, specifically hypoglycemic episodes. In a different meta-analysis of controlled studies, Boussageon *et al*. found little evidence that individuals with type 2 diabetes would benefit significantly from intensive glycaemic management in lowering DPN.[33]

Lifestyle and weight management

The Look AHEAD trial found that individuals with T2DM who were also obese or overweight and randomly allocated to receive a lifestyle intervention experienced a significant improvement in their questionnaire-based reports of DPN.[34] A thigh skin biopsy was used to quantify intra-epidermal nerve fiber branching, and other smaller studies employing more sensitive methods found lifestyle changes effective for delaying the development of DPN. Over 4 years, the sural and peroneal motor nerve conduction and the incidence of DPN significantly improved in patients who performed supervised aerobic exercise.[35] However, based on a crude neuropathy assessment utilizing the 10 g monofilament test (an assessment of light-touch perception and foot ulcer risk), the Diabetes Prevention Program Outcomes Study reported no such improvement. DPN may be one of the consequences of T2DM that bariatric surgery may help to reduce, but the evidence for this is currently limited.[28]

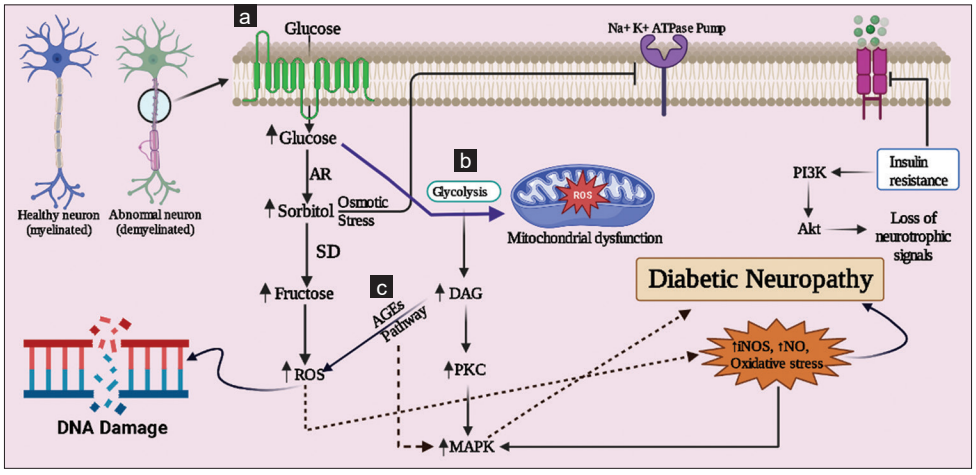

Figure 1: Pathways involved in the pathogenesis of diabetic peripheral neuropathy (DPN): Excessive glucose in the blood due to insulin insensitivity causes hyperglycemia, which leads to the upregulation of several pathways: (A) Polyol pathway: Excessive glucose converting into sorbitol and fructose cause osmotic stress and the formation of ROS, eventually leading to DNA damage. Osmotic stress also inhibits the $Na^{+}k^{+}$ATPase pump. (B) Glycolysis: Hyperglycemia causes hyperactivation of PKC and leads to upregulation of the production of MAPK; thus, DNA damage causes neuropathy. (C) AGE pathway: Here, upregulation of the AGEs pathways is caused by hyperglycemia, which disrupts energy regulation and decreases ATP production. These, in turn, increase oxidative stress, leading to the pathogenesis of diabetic neuropathy. (a) Above the glucose in fig (b) Glycolysis in the fig (c) AGEs Pathway

Tricyclic antidepressants

The effectiveness of tricyclic substances (TCAs) in DPN has been proven in several randomized controlled trials. TCAs have numerous adverse effects, including anticholinergic effects such as dry mouth, sweating, sedation, and vertigo. Starting the treatment with a low dose (10–25 mg) of either amitriptyline or imipramine at night will help with sleep because there is a nocturnal worsening of uncomfortable symptoms.[36] The dose is then gradually increased by adverse reactions and effectiveness. The risk of sudden cardiac death is also raised with TCA doses above 100 mg/day, according to recent results from a retrospective analysis with 58,956 person-years of TCA medication follow-ups. Thus, there is a strong case against giving TCAs to diabetic patients with cardiovascular disease. People with autonomic neuropathy should also take precautions to avoid having TCAs worsen their postural hypotension symptoms.[37]

Selective serotonin noradrenaline reuptake inhibitors (SNRIs)

Selective SNRIs reduce pain by enhancing the synaptic availability of noradrenaline and 5-HT in the descending pathways that block pain impulses. The effectiveness of duloxetine (an SNRI) in treating painful DPN has been examined in three identical trials, and combined data from these reveal that the 60 mg/day and 120 mg/day doses are beneficial in reducing painful symptoms, commencing within a week and lasting the complete treatment term of 12 weeks. A clinically significant pain alleviation was seen by 45–55% of patients with pain reductions of at least 50%.[38]

Aldose reductase inhibitors

The etiology of diabetic neuropathy has been linked to increased polyol pathway activity that results in sorbitol build-up. Aldose reductase inhibitors have attracted much interest as potential neuropathic pain therapies and as a means of preventing both painful and non-painful peripheral diabetic neuropathy.[39] Unfortunately, the results of these drugs' clinical studies have been unsatisfactory, either due to ineffectiveness or intolerable side effects. Up to 10% of individuals who took sorbinil experienced marked hypersensitivity and rashes, while those who took zenarestat and tolrestat experienced renal and liver toxicity, respectively.[40] A double-blind experiment with the new aldose reductase inhibitor fidarestat was recently finished in 279 patients. Although individuals with painful neuropathy were not the primary focus of this investigation, there was a reported decrease in the intensity of spontaneous pain and paresthesia while walking. There is a need for more research on painful neuropathy.[41]

PKC β inhibition

It is believed that increased PKC activity significantly contributes to the development of diabetic microvascular problems, with the PKC β isoform being identified as being of special significance. Microvascular dysfunction contributes to neuropathy, and in animal models, PKC β inhibition with the substance LY333531 reversed the microvascular and neurophysiologic deficits observed in the nerves of diabetic mice.[42] In these trials, diminished nerve conduction velocities and decreased sciatic nerve blood flow were restored to non-diabetic levels. A placebo-controlled clinical trial of LY333531 in 205 patients with

symptomatic DPN was conducted after these animal investigations. Using the neuropathy total symptom score-6 questionnaire (NTSS-6), the positive symptoms of numbness, allodynia, prickling, and pain (such as aching, burning, and lancinating) were evaluated both singly and as a TSS in this investigation. Both the 32 mg and 64 mg doses of LY333531 utilized were found to enhance the NTSS-6 significantly. To determine the effectiveness of this drug in treating patients with persistent painful DPN, a significant phase III multicenter clinical trial is now being conducted.[43]

CONCLUSION

While there are still many unexplored areas of DPN research, certain intriguing study possibilities could result in successful disease management. The pharmacological treatment of DPN remains a problem for clinicians despite the introduction of numerous therapeutic techniques in clinical use. Initial diagnosis of DPN is made using a few straightforward diagnostic techniques, and optimal glycemic management, which continues to be the cornerstone of prevention and a requirement for effective treatment, forms the basis of the subsequent therapy. Thus, a better therapeutic response may be attained by carefully addressing the underlying pathophysiology of the disease symptoms. The management of DPN is likely to continue to improve in the future through the use of novel therapeutic medicines that operate at the level of mitochondrial metabolic regulation. Since altered metabolic pathways are directly implicated in the etiology of DPN, research into medications that operate along these routes and the completion of comprehensive clinical trials may result in developing a curative therapy for DPN instead of a symptomatic alleviation with currently available conventional therapy.

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AUTHOR'S CONTRIBUTION

Mandeep Kaur wrote the manuscript, reading, data collection, and contribution. Prabha Rajput contributed to the designed review paper, data analysis, manuscript reading, and final approval.

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DECLARATIONS

Conflict of interest

The authors declare no conflict of interest.

Ethics approval and consent to participate

Not applicable because this is a review paper.

Consent for publication

All the authors agreed to the publication of the current review paper.

Availability of data and material

The manuscript has already provided all the data and material.

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