Review Article

Diabetic peripheral neuropathy essentials: a narrative review

Min Cheol Chang[1], **Seoyon Yang**[2]

[1]Department of Physical Medicine and Rehabilitation, College of Medicine, Yeungnam University, Taegu, South Korea; [2]Department of Rehabilitation Medicine, School of Medicine, Ewha Woman's University Seoul Hospital, Seoul, South Korea

Contributions: (I) Conception and design: MC Chang; (II) Administrative support: S Yang; (III) Provision of study materials or patients: MC Chang; (IV) Collection and assembly of data: MC Chang; (V) Data analysis and interpretation: S Yang; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: Seoyon Yang, MD, PhD. Assistant Professor, Department of Rehabilitation Medicine, School of Medicine, Ewha Woman's University Seoul Hospital, 260 Gonghang-daero, Gangseo-gu, Seoul 07804, South Korea. Email: mssyang@ewha.ac.kr.

Background and Objective: Painful diabetic peripheral neuropathy (DPN) affects approximately 6–34% of all patients with diabetes. DPN-induced pain reduces the quality of life and makes daily activities difficult. Distal symmetric polyneuropathy (DSPN) is the most common type of DPN. Here we review the pathophysiology, diagnosis, and treatment of DPN.

Methods: A MEDLINE database (PubMed) search was conducted for English-language articles dealing with the effect of DPN that were published until April 1, 2022. To identify potentially relevant articles, the following key search phrases were combined: 'diabetes mellitus', 'diabetes', 'neuropathy', 'polyneuropathy', 'diabetic neuropathies', 'peripheral neuropathy', 'diabetic polyneuropathy', 'pathophysiology', 'diagnosis', and 'treatment'.

Key Content and Findings: In a biopsy study of the sural nerve, damage to C and Aδ fibers were seen in patients who had recent onset of pain in their feet consisting of tingling, burning, and prickling, followed by initial demyelination/remyelination of large fibers. DPN is characterized by a pattern of distal-to-proximal axonal loss with symptoms. Hyperglycemia and dyslipidemia are the primary causes of DPN in patients with type 1 and 2 diabetes, respectively. The pattern of pain from DPN is described as "glove and stocking". DPN-induced pain is described as burning, electric, sharp, and dull aching with various pain intensities. DPN is a diagnosis of exclusion; diagnosis is made with a thorough medical history, physical examination, and clinical testing to rule out other causes of pain. Anticonvulsants (pregabalin and gabapentin), antidepressants (duloxetine, venlafaxine, and amitriptyline), opioids (tramadol, tapentadol, and oxycodone), and topical capsaicin are commonly administered to treat DPN. The combination of two or three of these pharmacological agents better resolves pain at lower doses and with fewer side effects.

Conclusions: Clinicians should have sufficient knowledge of DPN to ensure its accurate diagnosis and appropriate treatment. This review provides clinicians with the necessary knowledge of the pathophysiology, diagnosis, and treatment of painful DPN.

Keywords: Diabetes; neuropathy; diagnosis; pathophysiology; treatment

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Introduction

Diabetes is a serious chronic disease that significantly impacts well-being of people worldwide (1). It is also one of the top ten causes of main death in adults, with an estimated four million deaths worldwide in 2017. The global diabetes prevalence reached 9.3% (463 million people) in 2019 and is expected to increase to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045 (2). The increasing prevalence of diabetes has increased the incidence of chronic diabetic complications. Diabetic peripheral neuropathies (DPNs)

Table 1 The search strategy summary

Items	Specification
Date of search	April 1, 2022
Databases and other sources searched	PubMed
Search terms used	'diabetes mellitus', 'diabetes', 'neuropathy', 'polyneuropathy', 'diabetic neuropathies', 'peripheral neuropathy', 'diabetic polyneuropathy', 'pathophysiology', 'diagnosis', and 'treatment'
	Search term example: ["diabetes" AND ("peripheral polyneuropathy" OR "polyneuropathy")]
Timeframe	Until April 1, 2022
Inclusion and exclusion criteria	We selected articles on which were mainly about diabetic peripheral neuropathy. We then summarized the pathophysiology, diagnosis, and treatment of diabetic peripheral neuropathy. We excluded articles which were not in English. This review was limited to studies of human
Selection process	Two independent reviewers excluded articles after reading titles and abstracts (MCC and SYY) and full-text assessments were done to reject those ones not mainly on diabetic peripheral neuropathy. The reviewers attempted to resolve any disagreement by consensus

frequently occurs as a common chronic complication of diabetes (3,4). Distal symmetric polyneuropathy (DSPN) is the most common DPN, affecting about 50% of patients with type 2 diabetes after 10 years (5,6) and at least 20% of patients with type 1 diabetes after 20 years (7). Furthermore, DSPN may be present in approximately 20–25% of newly diagnosed patients with type 2 diabetes (8,9). Although the vast majority of DPN patients do not have pain, painful DPN affects about 15–30% of all patients with diabetes (10).

Painful DPN, like other chronic pain conditions, significantly decreases the patient quality of life (1). In addition, pain from DPN is often refractory to treatment, and various strategies are currently being attempted to manage it (11-13). As no single therapy or modality is effective or appropriate for every patient with DPN, the application of several alternatives for managing pain from DPN is required.

Here we review the pathophysiology, diagnosis, and treatment of DPN. We present the following article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-693/rc).

Methods

A MEDLINE database (PubMed) search was conducted for English-language articles dealing with the effect of DPN that were published until April 1, 2022. To identify potentially relevant articles, the following key search phrases were combined: 'diabetes mellitus', 'diabetes', 'neuropathy', 'polyneuropathy', 'diabetic neuropathies', 'peripheral neuropathy', 'diabetic polyneuropathy', 'pathophysiology', 'diagnosis', and 'treatment'. The summary of search strategy is provided in *Table 1*.

Pathophysiology of DPNs

Diabetes frequently affects the peripheral nervous system (14). The cell bodies of sensory neurons in the peripheral nervous system are located outside the blood-brain barrier. They are more vulnerable to diabetes-associated injury than motor neurons (15). Small unmyelinated neurons which are called as C-fibers are sensory neurons which comprise the majority of sensory neurons in the peripheral nervous system, carry nociceptive information, particularly about heat and pain (16). Due to the uniform distribution of ion channels along the axons of small unmyelinated neurons, a lack of myelin results in slow and continuous conduction (16). In addition, small, thinly myelinated Aδ fibers pass on information about pressure, touch, and cold. Fully myelinated fibers of different diameters, Aβ and Aα, referred to as large fibers, are responsible for vibratory and position sensing (17). Myelin, which is produced by Schwann cells, encases the axons of these fibers and forms the nodes of Ranvier and paranodes, which is needed for rapid nerve conduction and tight junctions (17).

Damage such as early degeneration and loss of C and Aδ fibers are observed in patients who recently developed pain in their feet consisting of tingling, burning, and prickling, followed by initial demyelination/remyelination of the large fibers (18,19). Also, large-fiber axonal loss

occurs in patients with diabetes, and patients suffer from loss of proprioception and numbness in the feet that move proximally over time (14). Diabetic neuropathy is characterized by distal-to-proximal axonal loss and accompanying symptoms (14). Although hyperglycemia is the primary cause of DPN in type 1 diabetes, dyslipidemia is the primary cause of DPN in type 2 diabetes (20-22). Diabetes causes glucose and free fatty acids to accumulate in Schwann cells (14). In hyperglycemic states, glucose moves to Schwann cells in excess via glucose transporter 3 and undergoes glycolysis. The resulting amount of pyruvate exceeds the metabolic handling capacity of the tricarboxylic acid (TCA) cycle, which leads to anaerobic metabolism and lactate accumulation (14). Lactate is subsequently moved from Schwann cells into axons, causing mitochondrial dysfunction and axonal degeneration. The increased substrate load of long-chain saturated fatty acids caused by dyslipidemia is associated with increased β-oxidation to form acetyl coenzyme A (14). Toxic acylcarnitine accumulates inside Schwann cells and is shuttled into the axons when the oxidation capacity of the TCA cycle is exceeded, which results in mitochondrial dysfunction and axonal degeneration (14). Small and large nerve fibers become energy-starved due to reduced mitochondrial function in the cell body, and long axons lose their functional ability and degeneration occurs. The axons farthest from the cell body become the most vulnerable (23). This vulnerability occurs as fewer functional mitochondria successfully travel long distances from the cell body to their most distal terminals along the entire axonal length (23). Small fibers that transmit pain and dysesthesia are vulnerable to energy loss in particular. Schwann cells can provide usable fuel, mitochondria, and protection from toxic substances to energy-starved large myelinated axons, but small fibers lack this energy source and protection (23). This might cause small fibers to be significantly degraded first.

Diagnosis of DPN

The most common clinical symptoms of DPN are symmetrical limb pain, a tingling sensation, and numbness, particularly at the distal end (i.e., DSPN) in the so-called glove and stocking pattern (14). Patients with DPN have described their pain as burning, electric, sharp, and dull ache, with pain intensities ranging from mild to severe (14). Approximately half of those with DPN experience worsening symptoms at night, when tired, or when stressed. In the advanced stages of DPN, weakness, poor balance, and unsteadiness can manifest (14). In addition, although the 10-g monofilament is frequently used for screening DPN in clinical practice, its use alone is not recommended because the light touch sensation loss develops in advanced DPN stages (24). Sensation tests that use pins and vibrations are more sensitive, and checking ankle reflexes is required because they are lost in the early stage of DPN (24). The diagnosis of DPN can be supported by a nerve conduction study. Especially, a nerve conduction study is important to exclude other causes of pain (25). Skin biopsy assessment of intra-epidermal nerve fiber density is considered as main method of diagnosis of diabetic neuropathy (26). DPN is a diagnosis of exclusion; diagnosis is made with a thorough medical history, physical examination, and clinical testing to rule out other causes of pain (*Table 2*) (27). Also, close monitoring of patients with diabetes for neuropathic symptoms is critical, as more than 10% reportedly do not mention their painful symptoms to their clinicians (28).

Chronic hyperglycemia is a major relevant factor in the etiopathogenesis of DPN (29); however, it is not clear whether the glycemic control is helpful in the management of painful symptoms. Previous studies have suggested that maintaining strict glycemic control is associated with lower pain severity (6,29). Although no randomized trials have evaluated the association between glycemic control and DPN progression, achieving optimal and stable glycemic control is an early step in DPN management. Dyslipidemia can increase oxidized low-density lipoprotein cholesterol and free fatty acid levels, which can increase levels of inflammatory factors or enhance inflammatory response signals (30). These pathways eventually damage neurons, glial cells, and vascular endothelial cells, resulting in DPN (20,22). Therefore, dyslipidemia should be controlled in patients with DPN.

The potential benefits of exercise for people with DPN were proven in several previous studies (31-33). The evidence on the effect of a structured exercise intervention program for type 2 diabetic patients is being considered as a moderate level 2 of evidence (34). A combination of aerobic and resistance exercises is usually applied (31-33). A meta-analysis of 11 clinical trials evaluating effects of exercise training on in type 2 diabetic patients and comparing those with controls was conducted (34). The mean difference of fasting inulin level was –1.64, fasting blood sugar –5.12, hemoglobin A1C 0.63, and body mass index –0.36.

Table 2 Various disorders that can cause bilateral distal peripheral neuropathy

Disorder	Symptoms
Diabetic peripheral neuropathy	Usually symmetrical and distally involved
	Initially involves the lower extremities
Chronic idiopathic axonal polyneuropathy	Occurs in older people
	Progresses slowly
	Usually symmetrical and distally involved
	Initially involves the lower extremities
Radiculopathy	Usually has aggravating factors, such as walking or sitting
	Pain can occur from buttock to calf
	Dermatomal distribution
Paraneoplastic syndrome	Triggered by an altered immune response to a neoplasm
	Causes distal neuropathic pain in the distal lower extremities
Vitamin B6 or B12 deficiency	Causes neuropathic pain in the distal lower extremities
Toxic neuropathy	Causes symmetrical and distally involved neuropathic pain after exposure to toxic materials
Vasculitic neuropathy	Involves skin lesions
	Frequently combined with motor weakness
	Asymmetrical involvement
Chronic inflammatory demyelinating polyneuropathy	Usually features motor weakness as well
	Upper extremities are also involved
Acquired immunodeficiency syndrome neuropathy	Combined with other symptoms related to acquired immunodeficiency syndrome
	Usually causes neuropathic pain in the distal lower extremities

Pharmacological treatments

Oral medication is often the first-line treatment for painful DPN. Various drugs can be used to manage DPN-induced pain (*Table 3*).

Anticonvulsants

Pregabalin and gabapentin are gabapentinoids are anticonvulsants that act by inhibiting the α2-δ calcium channels in the dorsal horn, thus inhibiting the release of pain-related neurotransmitters (35,36). Pregabalin is recommended as the first-line treatment by the American Diabetes Association; gabapentin is not approved for this indication (37). Pregabalin can control pain from DPN by reducing the release of glutamate and excitatory neurotransmitters, such as norepinephrine and substance P, starting at 50 mg/d and gradually increasing to 300 mg/d within one week based on its efficacy and tolerability (38). Side effects of pregabalin use included dizziness, somnolence, difficulty with attention and concentration, blurred vision, edema, and dry mouth.

Gabapentin is an anticonvulsant that is commonly used to treat pain from DPN; it is also considered a fist-line option (39). However, compared with pregabalin, gabapentin has some disadvantages, such as less flexible dosing, longer titration periods, and requirement for dosing adjustments in patients with renal impairment (40). Dosages for chronic pain begin at 300 mg/d and are gradually increased until adequate pain relief is achieved, with effective doses of 1,800–3,600 mg/d. The side effects of gabapentin include sedation, dizziness, somnolence, edema, and gait disturbance.

Antidepressants

Antidepressants including duloxetine, venlafaxine, and amitriptyline can effectively relieve DPN. Duloxetine and

Table 3 Pharmacotherapies for diabetic peripheral neuropathy-induced pain

Drug	Starting dose (mg/d)	Dose range (mg/d)	Mechanism	Side effects
Pregabalin	50	300	Calcium channel block	Dizziness, somnolence, difficulty with attention and concentration, blurred vision, edema, dry mouth
Gabapentin	300	1,800–3,600	Calcium channel block	Sedation, dizziness, somnolence, edema, gait disturbance
Duloxetine	60	120	Inhibition of norepinephrine and serotonin reuptake	Drowsiness, nausea, constipation, loss of appetite
Venlafaxine	75	75–225	Inhibition of norepinephrine and serotonin reuptake	Nausea, somnolence, constipation, loss of appetite
Amitriptyline	10–25	100	Inhibition of norepinephrine and serotonin reuptake	Dry mouth, drowsiness, orthostatic hypotension, urinary retention, constipation, visual disturbance
Tramadol	200	400	μ-opioid receptor agonism and inhibition of norepinephrine and serotonin reuptake	nausea, vomiting, constipation, dizziness, sweating, and dry mouth
Tapentadol	100	100–250	μ-opioid receptor agonist and inhibition of norepinephrine reuptake	Nausea, vomiting, dizziness
Oxycodone	37	120	Opioid agonist	Nausea, constipation, dizziness, headache, somnolence, fall, seizures, difficulty breathing
Topical capsaicin	1–4 applications of 8% patch for 30 min	1–4 applications of 8% patch for 30 min	TRPV1 agonist	Burning pain in the treated area, allergic reaction

TRPV1, transient receptor potential vanilloid 1 receptor.

venlafaxine are norepinephrine and serotonin reuptake inhibitors (41,42). Their endogenous analgesic effects are regulated by norepinephrine via downside inhibition (43). Duloxetine and venlafaxine manage chronic neuropathic pain by enhancing noradrenergic and serotonergic neuron activity in the descending pathway of the dorsal horn (41,42,44). These descending neurons inhibit dorsal horn neuron activity, preventing excessive pain-related input from reaching the brain.

Duloxetine was approved by the Food and Drug Administration as the first agent for treating DPN-induced pain (45). It inhibits norepinephrine and serotonin reuptake at rates 8.8 and 3.5 times greater than those of venlafaxine, respectively (46). It can also induce higher central norepinephrine concentrations and produce an analgesic effect (46). The starting dose of duloxetine was 60 mg/d, which was gradually increased to an effective or maximum tolerated dose (120 mg/d). The common side effects of duloxetine include drowsiness, nausea, constipation, and loss of appetite. In addition, its long-term use can significantly increase blood sugar. Venlafaxine doses of 75–225 mg/d were used to control pain from DPN. Venlafaxine is mechanistically similar to duloxetine (47). Adverse effects such as nausea, somnolence, constipation, and loss of appetite can occur.

Amitriptyline is a tricyclic antidepressant that exerts γ-aminobutyric acid (GABA)-related pain-reducing effects (48). GABA disinhibition is an important mechanism for controlling neuropathic pain (49). Amitriptyline is administered at a 10–25 mg/d starting dose and can be gradually increased to the effective or maximum tolerated dose (100 mg/d). Dry mouth, orthostatic hypotension, drowsiness, constipation, urinary retention, and visual disturbances are common side effects. In the treatment of DPN, amitriptyline can significantly improve nerve conduction, reduce pain, and increase satisfaction (50). These effects of amitriptyline were reported by one in every three patients who received amitriptyline (50).

Opioids

Tramadol, tapentadol, and oxycodone are opioids that effectively control pain due to DPN.

Tramadol is a μ-opioid receptor-selective agonist that exerts analgesic effects by activating the peripheral and central opioid receptors (51,52). Tramadol also has analgesic properties due to its ability to inhibit the neuronal reuptake of serotonin and norepinephrine (51,52). Its recommended starting dose is 200 mg/d, and it should be slowly increased to the effective or maximum tolerated dose (400 mg/d). Common side effects of Tramadol are nausea, vomiting, constipation, dizziness, sweating, and dry mouth.

Tapentadol is a potent analgesic that combines the mechanisms of a μ-opioid receptor agonist and a norepinephrine reuptake inhibitor (53). Opioid effects inhibit ascending pain signals in the spine, while increased norepinephrine synaptic levels enhance descending inhibitory signaling (53). Although the Food and Drug Administration has approved the use of tapentadol for the treatment of DPN, the risks of chronic opioid treatment make its use controversial. The effective dose of tapentadol is 100–250 mg/d, with an initial dose of 100 mg/d. Adverse effects such as nausea, vomiting, and dizziness are the primary causes of its discontinuation. In addition, owing to the addictive nature of opioids, their use should be avoided in favor of alternative pain management options.

Oxycodone hydrochloride is a morphine-class opioid agonist with analgesic properties that acts on nerve receptors (54). It acts primarily as an analgesic by activating opioid receptors on the synaptic nerve cell membrane of the central nervous system (54). Opioid receptors are also found in the peripheral and sympathetic nervous systems, gastrointestinal cells, and reproductive system (55). Various side effects such as nausea, constipation, dizziness, headache, somnolence, falls, seizures, and difficulty breathing have been reported (55). The average dose of oxycodone is 37 mg/d, with a maximum dose of 120 mg/d. Similar to tapentadol, the addictive nature of opioids prevents its prescription as an initial treatment for DPN-induced pain.

Topical capsaicin

Topical capsaicin is sometimes used to treat pain from a variety of causes, and it works by antagonizing the transient receptor potential vanilloid 1 receptor (TRPV1) (56). Its topical application reduces the number of TRPV1-expressing nociceptive nerve endings in the affected area, thereby providing pain relief in patients with painful DPN (57). However, its use is limited because patients frequently experience burning pain when a capsaicin-containing patch is topically applied.

Nonpharmacological treatments

Transcutaneous electrical nerve stimulation (TENS)

TENS is a simple low-cost, non-invasive neuromodulation method that can be used to treat various types of neuropathic pain, including painful DPN, with few contraindications or adverse effects (58). During its application, patients receive electrical stimulation to the skin through adhesive electrodes using a variety of waveforms that are broadly classified as high-frequency (>50 Hz), low-frequency (>10 Hz), or burst (59). The mechanism of action of TENS has not been clearly elucidated, but several possible mechanisms have been suggested, including improved microcirculation, increased endorphin and enkephalin levels, increased expression of proteins such as calcitonin gene regulating protein and nerve growth factor, and reduced inflammation (60). Although it has a long history of clinical use, its pain-reducing effect for controlling DPN has not been clearly established.

Repetitive transcranial magnetic stimulation (rTMS)

Several studies have shown that rTMS effectively controls various types of pain, such as peripheral or central neuropathic and musculoskeletal pain (61-63). The mechanisms underlying this pain alleviation method have not yet been clearly demonstrated. However, several possible mechanisms have been suggested (61-63). Previous functional magnetic resonance imaging studies demonstrated that rTMS causes changes in several cortical and subcortical structures associated with pain modulation and processing, including the orbitofrontal cortex, anterior cingulate gyrus, medial thalamus, and periaqueductal gray matter (64,65). This suggests that rTMS can modify the abnormal excitation of pain-related brain structures, triggering cascades of analgesic synaptic events. Furthermore, in an animal study, cortical stimulation had antinociceptive effects by changing neuronal activity in the periaqueductal gray matter responsible for pain processing (66). Only one study has reported the effects of rTMS on painful DPN. In 2022, Yang *et al.* reported that high-frequency rTMS (10 Hz) on the left M1 lowered the pain degree one

day and one week after 10 sessions (13). Further studies demonstrating the pain-reducing effect of rTMS on DPN should be conducted.

Considering the complexity of DPN-associated pain and the high risk of side effects of pharmacological agents, especially when higher doses of medications are required and in a patient population with multiple comorbidities, combination therapy is often warranted (67). The combined use of two or three pharmacological agents allows for better pain resolution at lower doses with better tolerance. Similarly, combining pharmacological and nonpharmacological treatment options may be more effective in patients with painful DPN.

Conclusions

Clinicians commonly encounter patients with painful DPN. Thus, they should have sufficient knowledge of DPN to ensure its accurate diagnosis and appropriate treatment. This review provides clinicians with the necessary knowledge of the pathophysiology, diagnosis, and treatment of painful DPN.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-693/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-693/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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