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Review

Current approach to diabetic polyneuropathy: current diagnosis and treatment

Hilal Yaşar[1], Aydın Çifci[2]

[1]Department of Neurology, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey
[2]Department of Internal Medicine, Faculty of Medicine, Kırıkkale University, Kırıkkale, Turkey

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Corresponding Author: Hilal Yaşar, hilal_ysr_96@hotmail.com

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ABSTRACT

Diabetes mellitus and its associated neuropathy are among the leading problems affecting the quality of life negatively. Diabetic foot problems due to neuropathy cause very serious problems. Physicians may focus too much on blood sugar regulation and ignore examinations for other macro and microvascular complications of diabetes. Although it appears earlier in patients with impaired blood sugar regulation, neuropathic symptoms are seen in almost half of diabetic patients who generally exceed 10 years. With early diagnosis and treatment, the quality of life of patients increases significantly. We touched on this issue in order to raise awareness of neuropathy, which is so common.

Keywords: Diabetes mellitus, neuropathy, polyneuropathy

INTRODUCTION

Diabetes mellitus (DM) is a collective term used to describe a group of diseases that result in high blood sugar resulting from a deficiency in insulin secretion or a defect in the action or response of insulin. Globally, the number of people with diabetes has quadrupled over the past three decades, making diabetes the ninth leading cause of death.[1] Worldwide, one in every eleven adults has DM, and 90% of them have type 2 DM.[2,3] Because of many epidemiological changes such as dietary habits, urbanization and the sedentary lifestyle that comes with it, type 2 DM is increasing in every region of the world, especially in low- and middle-income countries.[4] It is estimated that type 2 DM will affect 366 million people worldwide by 2030.[5]

Most patients with type 2 DM have at least one complication.[1] Peripheral neuropathies are one of the most important chronic complications of diabetes mellitus, together with nephropathy and retinopathy. Diabetic polyneuropathy (DPN) is the most common form of a group of diabetes-related neuropathies that include focal neuropathies and autonomic neuropathy. DPN is associated with sensory changes, loss of sensation, balance disorder and pain in the distal parts of the extremities, all of which impair patients' quality of life.[7-9]

DIABETIC NEUROPATHY

Diabetic neuropathy is a clinical or subclinical disease of peripheral nerves that occurs as a result of diabetes with no other underlying cause. It can affect the somatic and/or autonomic nervous system.[6] It is characterized by loss of sensory function starting distally in the lower extremities, as well as pain and severe morbidity. Over time, at least 50% of diabetic individuals develop diabetic neuropathy. While controlling the blood glucose level effectively stops the progression of diabetic neuropathy in patients with type 1 diabetes mellitus, this effect is lower in patients with type 2 diabetes mellitus.[19]

The risk of diabetic neuropathy increases with the following risk factors, indicators and comorbidities:[6]

- Diabetes duration
- Diabetes control (hyperglycemia)
- Arterial hypertension
- Peripheral artery disease
- Mönckeberg's sclerosis
- Diabetic retinopathy and nephropathy
- Depression
- Visceral obesity
- Hyperlipidemia
- Alcohol and/or nicotine use
- Insufficient physical activity
- Demographic factors (age, height, weight)

It is known that neuropathies developing in diabetic patients are a heterogeneous group of diseases with their symptoms, neurological involvement pattern, course, risk variables, pathological changes and underlying mechanisms.[10,11] The existing heterogeneity can be divided into at least two main subgroups; typical and atypical DPN.

Typical diabetic polyneuropathy is a chronic, symmetrical sensorimotor polyneuropathy with more prominent distal involvement and is thought to be the most common type of diabetic neuropathy.[10] Diabetic sensorimotor polyneuropathy (DSPN) develops with or against the background of long-standing hyperglycemia, associated metabolic disorders (increased polyol flux, accumulation of advanced glycation end

products, oxidative stress and lipid changes), and cardiovascular risk factors.[12-14] In addition to these, it has been observed that the microvessel changes observed in diabetic nephropathy and retinopathy are also associated with the pathological changes of the nerves affected in neuropathy. Over time, patients may develop autonomic dysfunction and neuropathic pain.[10,13]

Atypical diabetic polyneuropathies differ from DSPN in many important features, such as onset, course, mode of presentation, associations, and perhaps putative mechanisms.[15-17] Atypical DPNs can occur at any time during diabetes mellitus. The onset of symptoms may be acute, subacute, or chronic, while the course is usually monophasic or may fluctuate. Pain and autonomic symptoms are typical features.[15,17]

Among the types of diabetic neuropathy, far more studies have been conducted on distal symmetrical polyneuropathy, diabetic autonomic neuropathies, and especially cardiovascular autonomic neuropathy.[20-23] Atypical DPNs have been less characterized and studied.[18] Neuropathies similar to diabetic neuropathies may develop in prediabetic patients. Diabetic neuropathies are summarized in **Table 1**.[24]

Table 1. Classification of diabetic neuropathies[24]

Diabetic Neuropathies

A. Diffuse Neuropathy
• Diabetic sensorimotor polyneuropathy
  • Mixed sensorimotor neuropathy
  • Predominant large fiber neuropathy
  • Predominant small fiber neuropathy
  • Pure small fiber neuropa**thy**
• **Autonomic neuropathy**
  • Cardiovascular autonomic neuropathy
  • Decreased heart rate variability
  • Tachycardia while resting
  • Orthostatic hypotension
  • Exercise intolerance
  • Silent myocardial ischemia
  • Sudden c**ardiac death**
• **Gastrointestinal autonomic neuropathy**
  • **E**sophageal dysmotility
  • Gastroparesis
  • Diabetic diarrhea
  • Constipation (colon atony)
  • Fecal incontinen**ce**
• **Urogenital autonomic neuropathy**
  • Neurogenic bladder
  • Sexual dysfunctio**n**
• **Sudomotor dysfunction**
  • Peripheral anhidrosis
  • Hyperhidrosis
  • **Gustator sweating**
• **Inability to recognize hypoglycemia**
• **Pupillary dysfunction**
B. Mononeuropathy (mononeuritis multiplex) (atypical forms)
• Isolated cranial nerve palsy (e.g. oculomotor nerve palsy)
• Isolated peripheral nerve palsy (e.g. ulnar, median, femoral, peroneal nerve palsy)
• Mononeuritis multiplex (may resemble polyneuropathy)
C. Radiculopathy or polyradiculopathy (atypical forms)
• **Radiculoplexus neuropathy**
  • **Lumbosacral polyradiculopathy**
  • **Proximal motor amyotrophy**
• **Thoracic radiculopathy**

Common Non-Diabetic Neuropathies in Diabetes
Compression neuropathies **Chronic inflammatory demyelinating polyneuropathy** **Radiculoplexus neuropathy** **Acute painful small fiber neuropathies (treatment-related)**

PATHOPHYSIOLOGY OF DIABETIC NEUROPATHY

Axons from motor neurons in the spinal cord transmit signals to the muscles, while axons from sensory neurons in the dorsal root ganglia receive signals from the skin and joints. Supporting these axons presents a unique challenge, as they are often 20,000 times longer than their corresponding cell bodies. Schwann cells provide supporting myelin for axons in the peripheral nervous system, but most sensory axons are unmyelinated, making them more susceptible to damage than motor axons.

The complex array of metabolic and vascular factors in diabetes shift the balance between nerve fiber damage and nerve fiber repair in favor of damage. This balance shift occurs in a fiber-selective pattern, preferably affecting more vulnerable distal sensory and autonomic fibers, leading to progressive loss of sensation underlying the clinical manifestations of diabetic polyneuropathy.

Studies have identified several mechanistic pathways believed to play a role in the pathophysiology of diabetic neuropathy (**Figure 1**).[26]

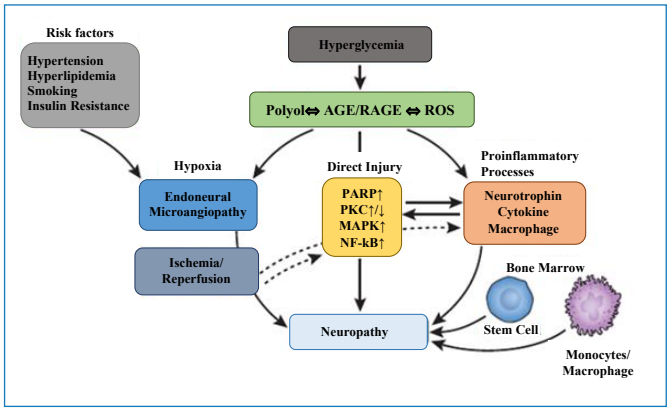

Figure 1. Summary of pathogenetic mechanisms of diabetic neuropathy[26]

Prolonged hyperglycemia causes downstream metabolic cascades of polyol pathway hyperactivity, enhanced glycation end products (AGE)/receptor for advanced glycation end products reactions (RAGE), and increased reactive oxygen species (ROS). Activation of poly-ADP-ribose polymerase (PARP) compromises both endoneural microvessels and neural tissues through activation of nuclear factor (NF-kB), as well as changes in protein kinase C (PKC) and an increase in mitogen-activated protein kinase (MAPK). They cause functional and structural changes in peripheral neuropathy.

Metabolic abnormalities in the nerve elicit proinflammatory reactions that induce the release of cytokines, suppression of neurotrophins and migration of macrophages and promote the development of neuropathy. There is also the possibility that other cellular components from the bone marrow may have an effect on neuropathology in diabetes. In addition, ischemia/reperfusion can accelerate nerve damage, which is partially mediated by inflammatory reactions. Risk factors represented by hypertension, hyperlipidemia, smoking and insulin resistance also contribute significantly to the development of neuropathy.[26]

NEUROPATHIC PAIN MECHANISMS

Neuropathic pain occurs as a result of permanent, maladaptive structural and functional changes in the somatosensory system after peripheral nerve injury. Experimental models of mechanical nerve injury have shown a loss of inhibition in the peripheral nervous system and central nervous system, as well as an increase in excitation and fasciculation of pain signals. However, while some individuals with diabetic neuropathy develop pain, the mechanism of the asymptomatic course of other individuals

with similar neuropathy levels is not fully understood. Neurophysiological measurements, molecular pathways and pathological findings do not fully explain the presence of neuropathic pain in DM. Therefore, the current view indicates that a complex interaction of risk factors (environmental and genetic), vascular and metabolic abnormalities (glycemic flow, metabolic syndrome, vascular injury and/or dysfunction) and psychosocial factors leads to peripheral and central nervous system maladaptations. The mechanisms suggested causing painful diabetic polyneuropathy are described in **Table 2**.[27]

Table 2. Mechanisms of painful diabetic peripheral neuropathy
Minor fiber damage
Autonomic dysfunction and vascular changes
Inflammation and immune system changes
Methylglyoxal
Ion channel dysfunctions
Central sensitization

CLINICAL AND DIAGNOSTIC METHODS

The earliest manifestations of diabetic polyneuropathy probably reflect the gradual loss of integrity of both large myelinated and small myelinated and unmyelinated nerve fibers.[28] Function, symptoms and examination findings according to the affected fiber are summarized in **Table 3**.[31]

Table 3. Affected fiber, function, symptoms and examination findings		
	Large Myelinated Nerve Fibers	**Small Myelinated Nerve Fibers**
• Function • Symptoms • Examination (clinically diagnostic	• Pressure, balance • Hypokinesis (abirritation), tingling, poor balance • Ankle reflexes: decreased/absent • Vibration perception: decreased/absent • 10 g monofilament: reduced/absent Proprioception: decreased /absent	• Nociceptive, protective feeling • Pain: burning, electric shock, stabbing • Thermal (cold/hot) discrimination: reduced/absent Pinprick sensation: decreased / absent

The main symptoms of diabetic polyneuropathy include negative symptoms such as numbness and loss of balance (related to nerve fiber loss or dysfunction) and positive symptoms such as tingling and pain (related to abnormal function of nerve fibers that remain unaffected). Symptoms begin distally in the toes and feet, and positive symptoms often worsen at night. Up to half of patients with diabetic polyneuropathy may be asymptomatic, but physical examination reveals mild to moderately severe sensory loss. Decreased or absent ankle reflexes occur early in the disease, while more diffuse reflex loss is a late finding.[28]

With the progression of the disease, loss of sensation increases and when it comes to the middle of the distal lower extremity, loss of sensation appears in the hands. This gradual evolution causes the typical "sock-glove" sensory loss. Diabetic polyneuropathy often begins insidiously and can lead to foot ulcers and muscle and joint disease. Distal motor axonal loss causes atrophy of the intrinsic foot muscles and an imbalance between the strength of the finger extensors and flexors. This leads to chronic metatarsal-phalangeal flexion (claw toe deformity) that shifts weight to the metatarsal heads. This weight shift results in the formation of calluses, which can crack, become infected, and ulcerate.[28]

Early recognition and appropriate management of neuropathy in patients with diabetes is important:[29]

1. Diabetic neuropathy is a diagnosis of exclusion. Non-diabetic neuropathies may be present and treatable in patients with diabetes.
2. Up to 50% of diabetic peripheral neuropathy may be asymptomatic. If not recognized and preventive foot care applied, patients are at risk of injury.
3. Recognition and treatment of autonomic neuropathy can improve symptoms, reduce sequelae, and improve quality of life.

Patients with type 1 diabetes for 5 years or more and all patients with type 2 diabetes should be evaluated annually for diabetic polyneuropathy using medical history and simple clinical tests.[29] Diagnosis of diabetic polyneuropathy is primarily made clinically. Evaluation of patients includes a detailed history and physical examination focusing on cardiovascular and neurological testing, and detailed evaluation of the feet.[30]

The clinical tests used to assess small and large fiber function and protective sensation are summarized in **Table 4**:

Table 4. Evaluation tests	
Evaluated Functions	Evaluation Tests
Small fiber function	Pinprick test and sensation of temperature
Large fiber function	Vibration perception (128 Hz diapason) and 10 gr monofilament test
Protective sense	10 g monofilament test

These tests not only screen for the presence of dysfunction but also predict the risk of future complications. Electrophysiological tests for screening or referral to a neurologist are rarely required, except when clinical features are atypical, the diagnosis is unclear, or a different etiology is suspected. Atypical features include motor involvement rather than sensory neuropathy, rapid onset, or asymmetrical presentation.[24,29]

Nerve conduction studies form part of the evaluation of diabetic polyneuropathy in atypical cases with concomitant compression neuropathy or inflammatory demyelinating neuropathy and in patients with minimal or no neurological findings. While nerve conduction studies are helpful in diagnosing patients with large fiber neuropathy, they are of limited use in diagnosing small fiber neuropathy. Small fiber function can be evaluated by skin biopsy and determination of intra-epidermal nerve fiber density, especially when results are normal. Decreased intra-epidermal nerve fiber density is indicative of small fiber neuropathy.[30]

DIABETIC NEUROPATHY TREATMENT

Patients with diabetic neuropathy should be treated in a systematic, incremental approach, including symptomatic treatment of pain where available, including education in glycemic control and metabolic syndrome control, foot care, and safety precautions. The treatment can be examined under two separate headings as preventive care and pain treatment.[31]

A. Preventive Maintenance

Symptomatic diabetic neuropathy is usually not reversible, and treatment is aimed at slowing further progression and preventing complications such as diabetic foot ulcers, arthropathy, and falls (**Table 5**).[31]

Table 5. Preventive maintenance methods
Glycemic Control
• The role and importance of glucose control in slowing the progression of neuropathy and other microvascular complications of diabetes varies by type of diabetes. • Good glycemic control plays a role in preventing the onset and progression of polyneuropathy in patients with type 1 diabetes mellitus. • In patients with type 2 diabetes mellitus, however, glycemic control is thought to have little or no effect on neuropathy.
Risk Factor Modification
• Lifestyle changes are considered a fundamental practice to prevent the onset and progression of neuropathy, especially in individuals with prediabetes and type 2 diabetes. • Goals include achieving a normal body weight and achieving individualized glycemic, blood pressure, and lipid goals, as well as 150 minutes of moderate to vigorous aerobic activity per week.
Foot Care
• Peripheral neuropathy is one of the most important risk factors for ulcers and amputations in patients with diabetes. Foot care in patients with neuropathy is essential to help reduce the risk of complications.

B. Pain Treatment

About 15 to 20 percent of patients with diabetic neuropathy have pain in the feet, often described as burning or stabbing, as a sign of small myelinated fiber involvement. While the pain may be self-limiting and resolve within a year of onset in half of the patients, the other half have persistent pain-related symptoms. Symptomatic treatments for neuropathic pain are an important component of treatment in such patients. Pain medications are not helpful for non-painful symptoms of neuropathy, such as drowsiness.[31]

The American Academy of Neurology (AAN), the European Federation of Neurological Societies (EFNS), the Neuropathic Pain Special Interest Group of the International Society for the Study of Pain (NeuPSIG IASP), and the National Institute for Health and Care Excellence (NICE) recommend that first-line drugs for the treatment of calcium channel a2- agrees that d ligands (gabapentin and pregabalin) and antidepressants that inhibit the reuptake of serotonin-noradrenaline. Some patients may benefit from opioids or topical treatment with capsaicin or transdermal lidocaine (**Figure 2**) (**Table 6**).[32]

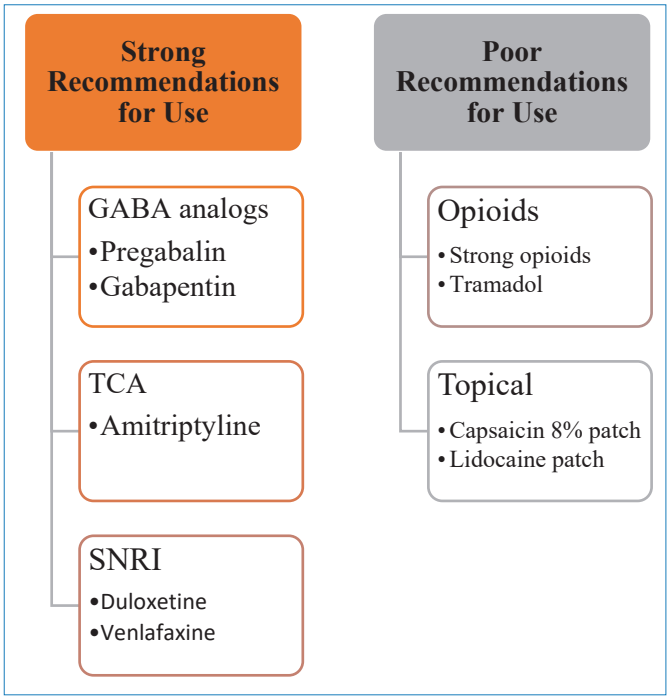

Figure 2. First-line drugs for the treatment of DNP

CONCLUSION

The prevalence of obesity and diabetes is increasing all over the world. As the average human life expectancy increases, the number of years spent with diabetes also increases. Chronic complications occur in diabetic patients over the years. It is known that almost more than half of diabetic patients for more than 10 years develop diabetes-related neuropathy. Diabetic neuropathy both reduces the quality of life with the symptoms it causes and can cause many health problems, especially diabetic foot. While focusing on blood sugar regulation of patients, it is important to screen for diabetic neuropathy and other chronic complications, and to approach treatment if detected. It is very important to inform patients about the development of such complications in order to prevent more serious situations in the future.

Table 6. Medications used in treatment DNP (adapted from source 32)

	Total Daily Dose and Dosing Regimen	Suggestions	Effewct Mechanism
Gabapentin	1200–3600 mg in three divided doses	First step, sufficient trial 3-8 weeks	Binds to voltage-gated calcium channels and reduces synaptic release of some neurotransmitters
Gabapentin, prolonged-release	1200-3600 mg, in two divided doses	First step, sufficient trial 3-8 weeks	
Pregabalin	300-600 mg in two divided doses	First step, sufficient trial 6-8 weeks	
Duloxetine	60-120 mg, once a day	First line, adequate trial 4-6 weeks	Inhibition of noradrenaline and serotonin reuptake potentialization of inhibitory pain pathways
Venlafaxine, prolonged-release	150-225 mg, once daily	First line, adequate trial 4-6 weeks	
Tricyclic c	25-150 mg, once or twice daily	First step, adequate trial 6-8 weeks	Noradrenaline and serotonin reuptake inhibition
Tramadol	200-400 mg in two or three divided doses	Second line, adequate trial 4-6 weeks	Partial μ-receptor agonist, Noradrenaline and serotonin re-uptake inhibition
Strong opioids	Individualized dosage	Third line, adequate trial 4-6 weeks	
Capsaicin 8% patch	1-4 patches to the painful area for 30-60 minutes every 3 months	Second line, (peripheral neuropathic pain)	Substance P depletion
Lidocaine patch	1-3 patches to the pain area once a day for up to 12 hours	Second line (peripheral neuropathic pain), adequate trial 3 weeks	Local anesthetic

ETHICAL DECLARATIONS

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