ABSTRACT

Although diabetic peripheral neuropathy (DPN) affects up to 50% of patients with diabetes, it has in some respects been considered the “Cinderella” of microvascular complications of diabetes, receiving less attention than it deserves with regard to screening, early detection, treatment, and prevention.

The clinical manifestations of DPN are pain (often experienced as burning, tingling, or allodynia) and insensitivity, which dramatically increases the risk for burns, injuries, and foot ulceration.

Risk factors for DPN include poor glycemic control, duration of diabetes, hyperlipidemia, elevated albumin excretion rate, and increased body mass index. DPN also is associated with cardiovascular disease and mortality and is second only to macroangiopathy as an independent risk factor for mortality.

The pathogenesis of DPN involves the progression of diabetes and chronic hyperglycemia to endothelial dysfunction via increased activity in 4 possible pathways: the protein kinase C pathway via diacylglycerol, advanced glycation end-product formation, the polyol pathway, and oxidative stress. Endothelial dysfunction, influenced by cardiovascular and genetic factors, progresses to microangiopathy and then to nerve hypoxia.

In clinical practice, detection of DPN begins with a careful history of sensory and motor symptoms, an inspection of the feet, and an evaluation of reflexes and sensory responses to vibration, light touch, pinprick, and the 10-g monofilament. Other tests to measure various thresholds are available as well.

Several drugs and nonpharmacologic modalities are available to treat painful DPN, but their efficacy and tolerability vary. Recent evidence of central nervous system involvement in DPN may open new avenues of investigation for the development of rational therapies.

The promise of the aldose reductase inhibitors in the treatment of DPN has not been fully realized. Newer aldose reductase inhibitors are undergoing clinical trials. Other interventions, such as α-lipoic acid and ruboxistaurin, show promise in reducing pain. In addition, according to study results, ruboxistaurin appears to have beneficial effects on nerve impairment and pain symptoms in patients with DPN.

Diabetic peripheral neuropathy (DPN), a microvascular complication of diabetes, is associated with considerable morbidity, mortality, and diminished quality of life. Characterized by pain, paresthesia, and sensory loss, it affects up to 50% of patients with diabetes, with new cases occurring at an annual incidence of about 2%. In absolute numbers, against the estimated global prevalence of 220 million cases of diabetes by 2010, DPN is likely to affect as many as 110 million persons worldwide—and at tremendous cost. In the United States alone, the total cost associated with DPN is $10.9 billion a year.

Diabetic peripheral neuropathy is the main predisposing factor for foot ulceration and infection. Foot
ulceration alone occurs in 15% of patients with diabetes during their lifetime and is the most common cause of hospital bed occupancy in the United States and abroad. With an annual incidence that ranges from 1% to 3%, diabetic foot ulceration accounts for a 15-fold increase in the likelihood of lower limb amputation in patients with diabetes versus nondiabetic people, and a 2-fold increase in mortality. Of those patients with diabetes who have had a lower limb amputated, more than 50% required amputation of the contralateral limb within 1 year.

From these epidemiologic data, DPN and diabetic foot ulceration clearly are far from rare, far from benign, and pose a major healthcare challenge to the medical profession and to society. However, in some respects, DPN is the “Cinderella” of diabetic microvascular complications, receiving less attention than it deserves in terms of screening, early detection, treatment, and prevention. New and emerging treatments for DPN, in addition to early detection and better control of hyperglycemia and other risk factors, soon may bring more attention to DPN.

**CLINICAL FEATURES OF DIABETIC PERIPHERAL NEUROPATHY**

Diabetic peripheral neuropathy, which is also referred to as distal symmetrical polyneuropathy, is the most common neuropathic syndrome seen in patients with diabetes. Less common neuropathic syndromes include cranial mononeuropathies and focal neuropathies such as proximal motor neuropathy.

Diabetic peripheral neuropathy starts in the toes and gradually moves upward. Once it is well established in the lower limbs, DPN affects the upper limbs, with sensory loss following the typical “glove and stocking” pattern of distribution. Significant motor deficits are not common in the early stages of DPN, although magnetic resonance imaging (MRI) examination of the lower limbs reveals atrophy of the small muscles of the foot as an early feature. Symptomatic muscle weakness, however, tends to develop later in the disease course.

Painful symptoms such as burning, tingling, and paresthesias are present early on in 30% of patients. Importantly, symptoms are not a reliable indicator of the severity of nerve damage. Some patients with severe pain symptoms have little sensory deficit, whereas other patients with no painful symptoms have completely numb feet, putting them at extremely high risk for foot ulceration.

Pain and insensitivity are the 2 clinical consequences of DPN. Pain symptoms, including burning, paresthesia (“pins and needles”), hyperesthesia, and allodynia (contact pain), can be extremely distressing and are typically worse at night. Pain can range from tingling in one or more toes to severe and persistent neuropathic pain. Patients commonly describe their symptoms as “sharp electric shocks that shoot up my legs” or “stepping on broken glass.” Others complain of disrupted sleep and pacing the floor during the night to distract themselves from the pain. Still, others voice frustration and depression because of the pain. Some patients, in fact, have committed suicide because of intractable and persistent neuropathic pain.

Insensitivity, or loss of pain, can lead to foot ulceration and a host of unintentional, but serious injuries. Patients who have lost sensation in their hands cannot detect temperature and often burn themselves while cooking or ironing, for example, and also have difficulty handling small objects. Those patients who have lost sensation in their feet often sustain puncture wounds, friction wounds, and burns that can become infected and/or ulcerated and lead to amputation. However, with appropriate foot care, at least 50% of ulcerations can be prevented.

**RISK FACTORS FOR DIABETIC PERIPHERAL NEUROPATHY**

Studies in patients with type 1 or type 2 diabetes mellitus have shown that poor glycemic control is one risk factor for DPN. The EURODIAB IDDM Complications Study, which involved 3250 patients with type 1 diabetes mellitus from 31 centers in 16 European countries, found that DPN was related to both glycemic control and duration of disease. Although the 30% baseline prevalence of DPN was significantly related to glycosylated hemoglobin (HbA1c; P < .001), the prevalence varied from 17% to 41% after data were adjusted for duration of diabetes mellitus, with lower HbA1c levels associated with lower prevalence rates and higher levels associated with higher prevalence rates. However, even those with good glycemic control (HbA1c < 5.4%, equivalent to HbA1c of 7% in the Diabetes Control and Complications Trial) still developed microvascular disease, suggesting that factors other than glycemic control and disease duration are involved.
Follow-up data from the EURODIAB cohort of patients with type 1 diabetes mellitus revealed that traditional markers of macrovascular disease such as cholesterol and fasting triglyceride levels, albumin excretion rates, von Willebrand factor levels, and body mass index also were associated with the development of DPN.13 After excluding all patients with DPN at baseline and adjusting the data for HbA1c and duration of diabetes mellitus, the investigators found that values for all of these factors were significantly elevated in all of the 276 patients who developed DPN after 7 years of follow-up compared with the values for the 896 patients who did not develop DPN during the follow-up period.

There is also evidence that DPN, a microvascular complication of diabetes mellitus, is associated with cardiovascular disease and mortality. In a study of 132 patients with type 2 diabetes mellitus, 38 died during the 9-year follow-up period.14 Macroangiopathy was found to be the strongest independent risk factor for mortality, followed in descending order by DPN, albumin excretion rate, and HbA1c. In addition, postmortem studies conducted at King’s College Hospital in London have demonstrated that patients with DPN die of coronary artery disease (Personal communication, Michael Edmonds, MD, March 2003).

**Pathogenesis of Diabetic Peripheral Neuropathy**

Until recently, there were 2 schools of thought regarding the etiology and pathogenesis of DPN: metabolic versus vascular. Recent studies, however, have shown that vascular factors and metabolic interactions are involved at all stages of DPN.15

Current thinking on the pathogenesis of DPN can be summarized by the schematic shown in Figure 1. Diabetes leads to chronic hyperglycemia, which appears to stimulate 4 pathways directly or indirectly: advanced glycation end-product (AGE-RAGE interaction) formation, polyol pathway hyperactivity, oxidative stress, and protein kinase C (PKC) activation. Increased activity in these pathways leads to endothelial dysfunction, which in turn leads to microangiopathy and then to nerve hypoxia. The latter results in structural damage to the nerve and irreversible neuropathy or reduced nerve conduction velocity.15

Cardiovascular risk factors such as hyperlipidemia, hypertension, smoking, and increased body mass index are major and independent contributors to endothelial dysfunction. Genetic factors may play a role as well, which may explain why some diabetic patients with good glycemic control develop microvascular complications while others with poor glycemic control do not. Similarly, cardiovascular risk factors contribute to microangiopathy, which is also influenced by coagulation and hematologic factors.15

Some of the vascular and metabolic interactions that occur in the pathogenesis of DPN are described below to help define the process further and to outline the rationale for new and emerging therapeutic interventions.

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**Figure 1. Pathogenesis of Diabetic Peripheral Neuropathy**

![Diagram](https://via.placeholder.com/150)

AGE = advanced glycation end-products; BP = blood pressure; BMI = body mass index; DAG = diacylglycerol; DM = diabetes mellitus; HbA1c = glycosylated hemoglobin; NO = nitric oxide; PKC = protein kinase C; RAGE = receptors for advanced glycation end-products; RBC = red blood cells.
In 1966, Gabbay et al proposed that sorbitol accumulation was a cause of DPN. In the polyol pathway, glucose is converted to sorbitol by the enzyme aldose reductase, and sorbitol to fructose by the enzyme sorbitol dehydrogenase. The key enzyme is aldose reductase. Later studies showed that aldose reductase inhibitors were able to increase nerve conduction velocity in animals, and to a lesser extent in humans, and that these agents produced some increase in nerve fiber counts in patients with DPN. However, there was no unequivocal improvement in terms of lessening signs and symptoms. Newer aldose reductase inhibitors are currently undergoing clinical trials.

Nerve fiber loss is the cause of insensitivity in DPN. As revealed by fascicular biopsy of the sural nerve, nerve fibers in patients with diabetes but no DPN are more numerous than in those patients with diabetes with DPN (Figure 2). Sural nerve biopsies also reveal microvascular defects in the endoneurial vessels, such as gross basement membrane thickening, endothelial cell proliferation, and hypertrophy (Figure 3), in addition to reduced oxygen tension in patients with DPN, as compared with patients who have diabetes but do not have DPN. Similarly, photography of surgically isolated sural nerve reveals microvascular abnormalities in the epineurial arteries and veins (Figure 4), whereas fluorescein angiography reveals arteriosclerosis on the surface of the nerve and impaired blood flow in patients with DPN compared to patients with diabetes without DPN.

Impaired blood flow adversely affects nerve conduction velocity, as demonstrated in exercise studies. Exercise to 80% maximal heart rate will increase sural sensory nerve conduction velocity by about 5 m per second in healthy people and 4 m per second in patients with diabetes without DPN. The same exercise will not increase conduction velocity in those patients with DPN because the neuropathic nerve that is also arteriosclerotic is unable to increase blood flow in response to exercise.

A more recent study of changes in sural nerve blood vessels in acute diabetic neuropathies such as acute insulin neuritis has shown that rapid improvement in blood glucose control can produce severe painful neuropathic symptoms. Acute insulin neuritis, once thought to be a metabolic condition, is, in fact, associated with proliferative changes that result in the development of a fine network of “neural new” blood vessels on the nerve surface—similar to the network of new blood vessels seen on the surface of the retina in patients with diabetes.

A recent study examining epineurial blood flow in patients with painful and painless DPN found that fluorescein levels rose more rapidly and epineurial intravascular oxygen saturation was significantly higher in patients with painful DPN compared to patients with painless DPN. These findings may reflect shunting from the endoneurium to the epineurium in patients with painful DPN and also support the premise that hemodynamic factors play a role in the pathogenesis of neuropathic pain.
In studying the effect of revascularization on nerve function in patients with DPN, Young et al examined groups of patients who had and had not undergone femoral popliteal bypass. The researchers found that both foot transcutaneous oxygen saturation and peroneal nerve multiconduction velocity increased significantly 6 weeks after surgery. However, in the control group of patients, there was no increase in either variable, demonstrating that improving blood flow to the limbs improves nerve conduction velocity.

**EARLY DETECTION OF DIABETIC PERIPHERAL NEUROPATHY**

Early detection of DPN is extremely important as it may result in earlier treatment and in prevention of further damage. In clinical practice, early detection begins with a careful history and an evaluation of sensory and motor symptoms, an assessment of disability resulting from the neuropathy, and the exclusion of conditions other than diabetes mellitus that may be causing the neuropathy.

The clinical examination should include a careful inspection of the feet; evaluation of ankle and knee reflexes; a sensory examination that includes testing for vibration, light touch, and pinprick sensations; the 10-g monofilament test to assess sensation in the foot; and an assessment of footwear, which is important because inappropriate or ill-fitting shoes are the most common form of trauma to the diabetic foot.

Some authorities advocate the additional use of a clinical scoring system that grades the degree of neuropathy on the basis of symptom, reflex, and sensory scores, such as the Toronto Clinical Scoring System that is weighted to emphasize sensory symptoms (Table). The scoring system has been validated and correlates well with electrophysiology findings and glycemic control.

The 10-g monofilament test is now standard for examination of the diabetic foot, is inexpensive and easy to use, and produces rapid and reproducible results. The test also predicts foot ulceration; those patients who cannot feel the monofilament are 15 times more likely to develop ulceration within 3 years than are those patients who have foot sensation.

However, there is some controversy regarding which and how many areas of the foot should be tested. Some groups suggest testing as many as 10 areas of the foot, but the group in Toronto that developed the scoring system advocates testing only the dorsum of the first toe in both feet. Within the 0 to 8 reference range, a combined score of 5 or above for both feet predicts DPN.

Another important test is the vibration perception threshold that detects subclinical neuropathy. It, too, is easy to use and predicts foot ulceration, with 0 to 5 volts indicating low risk, 16 to 25 volts indicating intermediate risk, and more than 25 volts indicating high risk. And, as demonstrated by

<table>
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<th>Table. Toronto Clinical Scoring System</th>
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<tr>
<td><strong>Symptom Scores</strong></td>
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<td>0–6</td>
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<tr>
<td>Foot pain</td>
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<tr>
<td>Numbness</td>
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<td>Tingling</td>
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<td>Ataxia</td>
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<td>Upper limb symptoms</td>
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Maximum score = 19.
0–6 = no neuropathy; 6–8 = mild neuropathy; 9–11 = moderate neuropathy; ≥ 12 = severe neuropathy.
Modified from Bril V, Perkins BA. Diabetes Care. 2002;25:2048-2052.
Coppini et al, the vibration perception threshold also predicts mortality, with higher death rates in diabetic patients with neuropathy than in diabetic patients without neuropathy.34

Other devices to measure the vibration perception threshold include the biothesiometer, the vibrameter, and the neuroasthesiometer. Efforts to standardize the equipment used for threshold measurement are currently under way.

More sophisticated equipment also is available to assess DPN and to detect thresholds for vibration, cooling, heat, and pain.35 However, to characterize DPN most accurately, nerve conduction velocity tests and staging the severity of neuropathy also are necessary.

TREATMENT OF PAINFUL DIABETIC PERIPHERAL NEUROPATHY

The current approach to management of painful DPN centers on achieving and maintaining near-normal glycemia (HbA1c) levels. However, many patients with diabetes, particularly those with type 2 diabetes mellitus, find this difficult.

Several drugs and nonpharmacologic modalities are available for pain relief, but efficacy and tolerability of adverse effects vary. For example, tricyclic antidepressants are effective in many patients but are associated with numerous adverse effects. Therefore, the starting dose, to be given at bedtime, should be low and can then be increased gradually or discontinued, depending on how effectively pain is relieved and whether the patient is tolerating the side effects.

Anticonvulsants such as gabapentin are also helpful,36 as is the opiate derivative tramadol.37 Although there may be a risk of addiction with tramadol, it is a useful drug to have in the armamentarium. Similarly, intravenous lidocaine and oral mexiletine, which are usually used to control cardiac arrhythmias, are often helpful in refractory patients.

Other drugs and nonpharmacologic approaches that are helpful in some patients include capsaicin cream, isosorbide dinitrate nasal spray, amantadine, acupuncture, and transcutaneous electrical nerve stimulation.

However, treatment of painful DPN is less than satisfactory, with some patients having severe adverse effects to therapy and others failing to respond at all to any of the above therapies.

A last resort for the treatment of refractory pain in DPN is spinal cord stimulation. After 3 years of follow-up in one study, patients reported that the stimulator markedly reduced both background pain and peak pain when it was turned on compared to when it was turned off.38 Over all, about 80% of patients responded to spinal cord stimulation; 20% did not respond, leading the investigators to explore whether abnormalities in the spinal cord itself could explain the lack of response.

Using MRI examination, the investigators found that the cross-sectional area of the cord was much smaller in patients with DPN than in control subjects and slightly smaller in those with DPN compared to patients with diabetes who did not have DPN.39 Although there was no statistically significant difference between the diabetic patients with DPN and without DPN, the study findings demonstrated spinal cord involvement in DPN. More recently, a large MRI study found significant spinal cord atrophy not only in patients with established DPN but also in those patients with subclinical DPN compared to patients with diabetes who did not have DPN.40 This study provides further evidence of spinal cord involvement in DPN.

More recent research provides evidence of neuronal dysfunction in the thalamus as a source of severe painful neuropathic symptoms (Unpublished observations). Clearly, a deeper understanding of the origins of these symptoms is needed to develop more effective therapies.

NEW INTERVENTIONS FOR DIABETIC PERIPHERAL NEUROPATHY

Although aldose reductase inhibitors, which reduce activity in the polyol pathway, generated considerable optimism about the treatment of DPN when first introduced in the 1980s, they have not demonstrated consistent efficacy or safety. Two of the inhibitors have been withdrawn from the market because of lack of efficacy, and 3 have been withdrawn because of allergic reactions, hepatotoxicity, or renal toxicity. Only one of this class of agents, epalrestat, is still on the market (in Japan), although new agents, including fidarestat, are being investigated in ongoing clinical trials.

Antioxidants have been used to treat DPN on the premise that they reduce activity in the polyol pathway. In the SYDNEY trial, α-lipoic acid 600 mg per day significantly lowered pain scores at 4 weeks compared to intravenous riboflavin.41 Thus far, α-lipoic acid, which is marketed in Germany, appears to be effective in reducing pain.
Ruboxistaurin, an inhibitor of the β isoform of PKC, is being studied in clinical trials involving patients with DPN and other microvascular complications of diabetes mellitus. In a phase II study of 205 patients with DPN and significant nerve impairment, preliminary results showed that ruboxistaurin 32 mg administered every day for 1 year markedly improved the composite score of 3 measures of nerve function from baseline compared to a placebo (Figure 5).42 The measures were the nerve impairment score of the lower limbs (representing the clinical examination), the nerve impairment score for the reflex examination, and the nerve impairment score of the lower limbs plus 4.

A preliminary subgroup analysis of 83 patients with clinically significant pain symptoms at baseline revealed marked improvement in pain scores after 6 months of treatment with ruboxistaurin 64 mg administered every day and after 1 year of treatment with ruboxistaurin 32 mg administered every day.43

As the study results indicate, ruboxistaurin appears to have beneficial effects on nerve impairment and pain symptoms in patients with DPN. Two large multicenter studies of this drug are under way, and reports of their results are awaited.

CONCLUSIONS

Diabetic peripheral neuropathy is a common disease, affecting up to 50% of patients with diabetes and accounts for considerable morbidity, mortality, and reduced quality of life.

Glycemic control is the central component of treatment but is difficult to achieve for many patients. Cardiovascular risk factors play a major role in diabetes mellitus and the pathogenesis of DPN and should also be controlled.

Painful neuropathy is difficult to treat. Because available therapies for pain and nerve impairment are less than satisfactory, rational therapies that address the underlying pathogenesis must be developed. Evidence that the central nervous system and vascular factors are involved in DPN should open new investigations for the development of effective therapies. At present, promising interventions that appear to be beneficial are being studied, and the results of the clinical trials are eagerly awaited.

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