Diabetic peripheral neuropathy (DPN), also referred to as distal symmetric polyneuropathy (DSP), is the presence of symptoms and/or signs of peripheral nerve dysfunction in patients with diabetes after other causes of dysfunction have been excluded. Diabetes mellitus is an important cause of peripheral neuropathy, accounting for almost half of all cases. The incidence of DPN is high in patients with diabetes, as shown by a population-based study conducted at the Mayo Clinic, which found that 47% of diabetic patients had DSP. Another study, which defined neuropathy as bilateral absence of ankle jerks and/or vibratory loss, reported a prevalence of 70% in patients who have had type 2 diabetes for 25 years or more. Given that the prevalence of diabetes in the United States is approximately 24 million persons, these studies suggest that at least 15 million Americans will develop DPN in their lifetime. If persons with pre-diabetes are included, this number may well exceed 20 million. Recent studies have estimated that the prevalence of painful DPN among diabetic patients is 20%. Extrapolating this percentage to the prevalence of diabetes suggests that almost 5 million persons in the United States have symptomatic DPN.

Many of these patients as well as the majority of those with painful DPN are unaware of their neuropathy. Painless neuropathy can be particularly dangerous because patients may not be able to detect an injury to the foot (eg, get burned from a hot bath, step on a sharp object, or develop a blister from a tight shoe). If not recognized and treated aggressively and quickly, these injuries may result in foot ulcers, infections, and even an amputation. For this reason, DPN is often referred to as the “forgotten complication” of diabetes.

Clinicians must be vigilant when examining the patient with diabetes to avoid overlooking this important microvascular complication. This article reviews the approach to evaluating patients for DPN, focusing on its major clinical presentations (ie, the painful or painless lower extremity), and discusses current management options.

RISK FACTORS

Nonmodifiable risk factors for diabetic microvascular complications, including DPN, are older age, genetic profile (eg, polymorphism of the aldose reductase gene), increased duration of diabetes, and height. Taller persons are more susceptible to developing DPN because they have longer peripheral nerves. Since men tend to be taller than women, it is not surprising that men are more commonly affected with DPN than women. Modifiable risk factors for DPN include hyperglycemia, hypertension, dyslipidemia, smoking, and heavy alcohol use. The European Diabetes Prospective Complications Study, a prospective multicenter study, reported that the development of DPN was highly correlated with both the duration of diabetes and the level of hemoglobin A1c. Other statistically significant potentially modifiable risk factors reported were levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides; body mass index; a history of smoking; hypertension; the presence of microalbuminuria; and...
cardiovascular disease. Although many physicians know that improved glycemic control can prevent or ameliorate DPN, most providers are unaware that similar improvements can be achieved by control of lipids and smoking cessation.

PATHOGENESIS

As with other diabetic microvascular complications, such as retinopathy and nephropathy, DPN is thought to result from multiple factors. Putative mechanisms for the development of DPN include glycosylation of neural proteins, microangiopathy, the development of neural autoantibodies, and ischemia from basement membrane thickening of the nerve capillaries (vaso nervorum). Abnormalities of the polyol pathway and defects in metabolism of myoinositol and protein kinase C3 leading to neuronal demyelination have also been described in DPN. Figure 1 shows the proposed pathogenic mechanisms and their interaction leading to clinical diabetic neuropathy. Why this disorder often leads to a clinical scenario of painful feet in the minority of cases and a painless neuropathy in the majority of cases is not understood.

EVALUATION AND DIAGNOSIS

Symptoms and History

Diabetic neuropathy may present as either a focal or diffuse type. Focal neuropathies, including entrapment neuropathy (eg, carpal tunnel syndrome), mononeuropathy multiplex, cranial neuropathies, plexopathies, and rarely polyradiculopathy, will not be addressed in this review. Diffuse neuropathy, or generalized polyneuropathy, is typically characterized by the predominant fiber type(s) involved: small-fiber sensory, large-fiber sensory, large- and small-fiber sensory, or sensorimotor polyneuropathy.

DPN often presents with neuropathic pain but can also present with decreased balance or a change in gait. The International Association for the Study of Pain has described neuropathic pain as “pain initiated or caused by a primary lesion or dysfunction in the nervous system.” However, a recent review proposed redefining neuropathic pain as “pain arising as a direct consequence of a lesion or disease of the somatosensory system.” Neuropathic pain is different in quality and onset from nociceptive pain, which patients can often link to a specific musculoskeletal or soft tissue injury. The neuropathic pain from DPN usually has a gradual and insidious onset and appears to arise de novo.

Three distinct types of pain have been described in patients with DPN. Dysesthetic pain is an unpleasant abnormal sensation, whether spontaneous or evoked, and often presents as severe burning or itching sensations. Paresthetic pain presents as a “pins and needles” sensation or an electric or knife-like shooting pain. Muscular pain presents as a deep, dull, aching or cramping pain that may be described as “night cramps.” Each of these types of pain may have a different pathogenesis and anatomical distribution. Although most patients have a mixed or “pansensory” neuropathy, occasionally patients present with selective involvement. Involvement of small sensory fibers often causes severe superficial burning pain, whereas involvement of large sensory fibers is more often associated with paresthesias, loss of ankles jerks, and decreased balance (Table 1).

In general, pain from DPN is worse at rest and in the evenings, possibly because the nervous system is not “distracted” in the evening by a multiplicity of other inputs (eg, visual, locomotory, or thinking) that
it is constantly processing during the day. Patients with diabetes whose pain is worse with walking or standing need to be evaluated for a concomitant disorder. It is classically symmetrical and distal. Since DPN is felt to be a “dying back” of the nerves, it affects the most distal extremities first, resulting in the “stocking and glove” distribution (Figure 2). Patients with DPN may experience allodynia, which is pain due to a stimulus that does not normally provoke pain (eg, severe pain caused by a bed sheet touching bare toes), or hyperalgesia, which is an increased response to a stimulus that is not normally painful (eg, pain occurring with light touch). Patients may also complain of other abnormal sensations, such as “my shoes feel too tight,” or describe a feeling of “walking on pebbles” or like their “feet are in ice water.”

Signs and Neurologic Examination

The physical examination in a patient with suspected DPN begins with inspection of the lower extremities. Observation may reveal dry and cracked skin and/or cold skin (despite good pulses) in patients with DPN. These abnormalities result from autonomic components of DPN, including loss of sweat glands and shunting of blood away from the skin. A characteristic finding on neurologic examination is loss of deep tendon reflexes. Ankle jerks are initially decreased and then lost. Knee jerks may be preserved until more advanced stages of the disease when the hands become affected. The 128 Hz tuning fork is the instrument of choice to check for the presence or absence of vibratory sensation in the feet. Initially, patients show deficits in vibration perception of the great toes, but over time the deficits move proximally to the metatarsophalangeal joints, dorsum of the foot, ankle, and the mid-tibial region.

Use of the Semmes-Weinstein monofilament has helped define degrees of sensory loss in the feet and hands of patients with DPN. To use the device properly, the examiner should place the tip of the monofilament perpendicular to the plantar surface of the great toe. Examiners should not allow the filament to slide across the skin or make repetitive contact to the site. Areas of callus must be avoided for an accurate exam. With their eyes closed, patients should be able to sense the monofilament by the time the monofilament buckles (Figure 3). The thicker (higher number) the monofilament, the more force is required to cause the buckle. Patients without neuropathy should be able to sense the 3.61 monofilament (equivalent to 0.4 g of linear pressure). The inability to sense monofilaments of 4.17 (equivalent to 1 g of linear pressure) or higher is considered consistent with neuropathy (large-fiber modality). The inability to sense a monofilament of

![Figure 1. Proposed mechanisms of diffuse diabetic neuropathy. (Adapted with permission from Tanenberg RJ, Schumer MP, Green DA, Pfeifer MA. Neuropathic problems of the lower extremities. In: Bowker JH, Pfeifer MA, editors. Levin and O’Neal’s the diabetic foot, 6th ed. St. Louis: Mosby; 2001.)](image-url)
5.07 (equivalent to 10 g of linear force) is consistent with severe neuropathy and loss of protective sensation. Unfortunately, most physicians are only familiar with or have access to the 5.07 monofilament, and there is a widespread misconception that DPN may be ruled out when a patient can feel this size device.

Small fiber nerve loss can be detected with pinprick, although a cold perception gradient loss (using hot and cold water-filled test tubes or the flat side of a tuning fork) may be easier to define than loss of pinprick perception. The last sensory modality to become abnormal in this distal gradient loss neuropathy is loss of joint position sense (proprioception). Unfortunately, this is an all too common finding in many patients with long-standing DPN.

Foot deformities are common findings in advanced cases of DPN. Although primarily a sensory disorder, DPN often includes an accompanying motor disorder that leads to the “hammer toe” or “claw foot” deformities (Figure 4). The loss of foot flexor strength allows the unopposed foot extensors to contract and pull the toes into a hammer or claw position. This deformity redistributes the weight on the often insensate metatarsal heads, greatly predisposing the neuropathic individual to ulceration. Other foot findings seen in patients with diabetic neuropathy include Charcot arthropathy, limited joint mobility, abnormal toe position, calluses, and partial foot amputations.

When DPN involves the hands, it typically occurs several years after affecting the lower extremities. Often patients have become completely insensate to the mid-tibia when their hands begin to lose feeling. Initially, most patients complain of paresthesias in the hands. Later, as the hands become weaker, patients may complain about dropping objects and deteriorating handwriting. Loss of muscle mass in the hands (wasting of the intrinsic hand muscles) becomes apparent.

### Laboratory Testing

The consensus definition of DPN requires ruling out other disorders that cause peripheral neuropathy before attributing the neurologic findings to diabetes (Table 2). Evaluation of the patient should include basic laboratory tests, such as a thyroid-stimulating hormone, serum protein electrophoresis, and vitamin B₁₂ level, to look for other causes of polyneuropathy. Patients with diabetes mellitus also commonly develop other diseases such hypothyroidism, B₁₂ deficiency, celiac disease, and uremia, all of which may cause or contribute to peripheral neuropathy. It should also be noted that prediabetes (previously called impaired glucose tolerance or impaired fasting glucose) may also present with DPN. In fact, neurologists will frequently order a glucose tolerance test when a patient presents with an idiopathic peripheral neuropathy.

### Diagnostic Testing

A good history and physical examination as described above are required to confirm sensory loss and to look for coexisting motor involvement. However, since DPN

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**Table 1. Clinical Features of Small and Large Fiber Diabetic Peripheral Neuropathy**

<table>
<thead>
<tr>
<th>Fiber Type</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small</td>
<td>Pain predominates, often burning and superficial; Allodynia (pain from normal stimuli such as bed sheets); Defective warm thermal sensation; Defective autonomic function; Decreased sweating (dry feet); Impaired vasodilatation (cold hands/feet)</td>
</tr>
<tr>
<td>Large</td>
<td>May involve sensory or motor nerves; Most distal nerves affected first: “stocking-glove” pattern; More neurologic signs than symptoms; Impaired vibratory perception; Depressed or absent deep tendon reflexes; Pain is deep—described as gnawing, like a toothache or even cramping</td>
</tr>
</tbody>
</table>

is a diagnosis of exclusion the clinician must consider non-neuropathic disorders as well as other causes of peripheral neuropathy (Table 2). If the patient’s neurologic findings are primarily in the upper extremities, more motor than sensory, or predominantly unilateral, DPN (if present) is most likely not the major diagnosis. In these cases, referral to a neurologist for electromyography and nerve conduction studies can exclude focal nerve entrapments, lumbar radiculopathy, chronic inflammatory demyelinating polyradiculoneuropathy, and other disorders. However, even these studies have limitations since they only assess large nerve fibers. A patient may have neuropathic pain and normal studies, or have abnormal studies with no pain. In these cases, additional sophisticated studies may be required to establish the diagnosis and recommend a treatment strategy.12

**TREATMENT**

Pain is primarily carried by unmyelinated C-fibers within the peripheral sensory nerves, which enter the dorsal horn of the spinal cord. Peripheral nerve injury causes the release of various neurotransmitters at the dorsal horn region, which in turn leads to an increased calcium influx into cells in a process known as central sensitization. Eventually the spinal cord becomes hypersensitive to afferent fibers. Although a detailed explanation of this phenomenon is beyond the scope of this article, an understanding of the central and peripheral mechanism for neuropathic pain helps to explain why different classes of drugs can be beneficial for treating neuropathic pain.13,14

**Pharmacologic Therapy**

Pharmacologic treatment of painful DPN is limited, since no drug will totally eliminate neuropathic pain. A drug is considered to have a successful response if it reduces a patient’s pain score by 50% (eg, decreases from 8 to 4). Some patients fail to respond to certain drugs, and others develop adverse effects even at the

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**Figure 3.** Semmes-Weinstein monofilament examination. The 5.07 monofilament can detect the presence or loss of protective sensation. This photo demonstrates the correct usage of the Semmes-Weinstein monofilament to detect neuropathy and to determine if protective sensation is lost. The patient should be comfortable and have his eyes closed. The monofilament buckles when the 10 g of linear force are applied by the examiner for about 10 seconds. Note that this patient has early claw toe deformities. He was insensate to the 5.07 and even the 6.65 monofilament. (Adapted with permission from Tanenberg RJ, Donofrio PD. Neuropathic problems of the lower extremities in diabetic patients. In: Bowker JH, Pfeifer MA, editors. Levin and O’Neal’s the diabetic foot, 7th ed. St. Louis: Mosby; 2008:51.)

**Figure 4.** Claw toes and neuropathic ulcer. This patient had a long-standing history of diabetic peripheral neuropathy with insensate feet. He developed bilateral claw foot deformity and then a neuropathic ulcer over the fifth metatarsal head of the right foot. The ulcer was treated by a podiatrist and healed. The patient now wears custom diabetic shoes to prevent a recurrence. (Adapted with permission from Tanenberg RJ, Donofrio PD. Neuropathic problems of the lower extremities in diabetic patients. In: Bowker JH, Pfeifer MA, editors. Levin and O’Neal’s the diabetic foot, 7th ed. St. Louis: Mosby; 2008:36.)
The goal of pharmacotherapy in DPN is not to eradicate pain; rather, a practical goal is to make it possible for the patient to get to sleep and stay asleep at night. The next goal should be to improve the patient’s daytime functioning and overall quality of life. Ideally, the treating physician should discuss these goals with the patient when the drug is initially prescribed. Table 3 lists the categories of drugs used for painful DPN. Note that only pregabalin and duloxetine have been specifically approved by the US Food and Drug Administration (FDA) for the treatment of painful DPN.

Nonsteroidal anti-inflammatory drugs and tramadol. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be helpful for some patients with mild pain from DPN who have normal renal function. A small (n = 18) single-blind study demonstrated that the NSAIDs ibuprofen and sulindac were better than placebo for painful DPN, with about half of patients having a good response. More effective than NSAIDS is the unique pharmacologic agent tramadol. This compound is both an opioid agonist and an activator of monoaminergic spinal inhibition of pain. Multicenter, randomized, double-blind placebo-controlled studies have found that patients receiving tramadol at an average daily dose of 210 mg/day had both statistically significant pain relief and improved physical and social functioning for up to 6 months.

Antidepressants. Tricyclic antidepressants (TCAs), a mainstay for the treatment of DPN for many years, are used less commonly today because of their significant anticholinergic side effects, especially in the elderly. Studies have demonstrated that the TCAs amitriptyline and desipramine provide moderate to good relief of pain in approximately 70% of patients with painful DPN. These drugs relieve pain independent of their antidepressant effects. When treating thin or elderly patients, it is best to start with a 10-mg dose at bedtime and to advance very gradually. Relief of pain may not occur until several weeks after treatment is initiated. Orthostatic hypotension, xerostomia, somnolence, and weight gain are common side effects that limit the use of this class of drugs.

A newer class of antidepressants includes duloxetine, a balanced selective serotonin-norepinephrine reuptake inhibitor. Duloxetine was the first drug approved by the FDA for use in the treatment of painful DPN. The drug has a half-life of 12 hours and can be given once daily. Randomized controlled clinical trials of duloxetine have demonstrated an excellent reduction in pain score, with less than 20% of patients discontinuing the drug because of adverse events. As opposed to TCAs, duloxetine does not cause weight gain. The most frequent adverse effects include nausea, constipation, dry mouth, and somnolence. The starting dose of 30 mg a day for the first week will minimize these side effects.

Anticonvulsants. The first-generation anticonvulsants such as phenytoin and carbamazepine are no longer used for painful DPN because they are less efficacious and have more side effects than the second-generation anticonvulsants. Gabapentin and its newer cousin pregabalin bind to the δ subunit of voltage-activated calcium channels. Pregabalin has a sixfold higher binding affinity than gabapentin. Also, pregabalin has over 90% bioavailability, which means that maximum pain relief occurs within 48 hours. Gabapentin has a very low bioavailability and the amount of the drug absorbed is dose dependent, with the fraction of dose absorbed decreasing with increasing doses.

Gabapentin must be given 3 times daily, whereas pregabalin can be used 2 or 3 times daily. The FDA approved pregabalin for painful diabetic neuropathy in a maximum dose of 300 mg/day, whereas it is approved for up to 450 mg/day for fibromyalgia and 600 mg/day for postherpetic neuralgia. Dizziness and somnolence are the major side effects of gabapentin. These same side effects are seen in pregabalin and are very much dose dependent. Pregabalin also can cause both edema (especially in patients taking a thiazolidinedione) and
weight gain. Experts have reported that patients who cannot control their pain on gabapentin have responded to equivalent doses of pregabalin.\textsuperscript{22} The conversion factor between these 2 drugs is 6:1 so that a patient taking 1800 mg of gabapentin would require 300 mg pregabalin for the comparable effect. Although gabapentin is available as a generic form, the higher doses required tend to minimize the cost saving over pregabalin.

Pregabalin is primarily eliminated from the systemic circulation by renal excretion as an unchanged drug with a half-life of approximately 6.3 hours. Both of these drugs must be given in much lower doses for patients with glomerular filtration rates under 60 mL/min. Because pregabalin can be removed by hemodialysis, a supplemental dose of 25 mg should be given following every 4-hour hemodialysis treatment.

**Combination therapy.** If the patient does not respond to the maximum strength formulation of any of the first- or second-line drugs, it is reasonable to use 2 or 3 different drugs together (eg, pregabalin and duloxetine plus either amitriptyline or tramadol). If combination therapy fails, referral to a pain clinic should be considered before prescribing narcotics such as controlled-release oxycodone.

**Alpha-lipoic acid.** It should be noted that none of the drugs described affect the underlying neuropathic process but rather provide symptomatic relief, which stops as soon as they are discontinued. The hope is that better glycemic control and smoking cessation can be accomplished while the pain is addressed. Several clinical trials have found that alpha-lipoic acid, available in the United States as an over-the-counter supplement, may actually ameliorate the underlying disease process as well as improve pain. In one study, doses of 600 mg 3 times daily for 5 weeks improved pain, paresthesias, and numbness.\textsuperscript{23}

### Table 3. Major Drugs for Treatment of Painful Diabetic Neuropathy

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Compound</th>
<th>Dosing, Start/Maximal (mg)</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCA</td>
<td>Amitriptyline, other TCA</td>
<td>10/150</td>
<td>Anticholinergic, sedation, weight gain</td>
<td>Use with caution in elderly</td>
</tr>
<tr>
<td>Weak opiates</td>
<td>Tramadol</td>
<td>50/400</td>
<td>Sedation, dizziness constipation</td>
<td>Generic formulation; can be taken every 6 hr</td>
</tr>
<tr>
<td>SSNR</td>
<td>Duloxetine</td>
<td>30/120\textsuperscript{a}</td>
<td>Somnolence, xerostomia, GI</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>Gabapentin</td>
<td>300/3600\textsuperscript{a}</td>
<td>Somnolence, ataxia, dizziness</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>Pregabalin</td>
<td>150/600\textsuperscript{a}</td>
<td>Somnolence, ataxia, dizziness, edema, weight gain</td>
<td>FDA approved</td>
</tr>
</tbody>
</table>

*GI = gastrointestinal; SSNR = selective serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressants.

\textsuperscript{a}Decrease dose if glomerular filtration rate is < 60 mL/min.

**Topical Products and Nonpharmacologic Therapy**

Topical products for the treatment of painful DPN include the 5% lidocaine patch and capsaicin, the active agent in hot peppers. When applied to skin over a prolonged period of time, capsaicin depletes substance P, an endogenous neuropeptide necessary for the propagation of pain. Unfortunately, the drug must be applied to the painful areas 4 times a day and most patients find it difficult to use. Likewise, the lidocaine patch, although often effective in treating an area on the trunk when used in treating postherpetic neuralgia, is difficult to use on the feet in patients with painful DPN.

Nonpharmacologic treatment includes physical therapy, transcutaneous electrical nerve stimulation, acupuncture, and psychological support. In patients with extremely refractory DPN, neurosurgical (spinal cord stimulation) and orthopedic (tarsal tunnel decompression) procedures have been performed to relieve pain.\textsuperscript{24,25}

**Treatment of the Insensate Patient**

The International Consensus of the Diabetic Foot has identified 5 key elements as cornerstones of foot management for the patient with diabetes.\textsuperscript{26} These include:

1. Regular inspection and examination of the foot
2. Identification of the foot at risk
3. Education of the patient, their family, and providers
4. Appropriate footwear
5. Treatment of nonulcerative pathology

Custom or modified footwear is critical in preventing ulceration in patients with insensitive feet, deformities, or a past history of a foot ulcer. To help in this
process, clinicians should refer patients with diabetes who need custom footwear to either an experienced podiatrist or certified pedorthist. Custom diabetic shoes can decrease the risk of ulceration rate from 60% to 20% over 3 years. In the United States, the Medicare-supported Therapeutic Shoe Bill allows for payment for special footwear and insoles made for people with diabetes who have a history and/or physical examination that identifies any of the following conditions: peripheral neuropathy with evidence of callus formation; previous amputation; previous foot ulceration; significant foot deformities; and circulatory compromise. The guidelines for custom diabetic footwear may be accessed at the Center of Medicaid and Medicare Services website.

SUMMARY

Diabetic neuropathy is a major public health problem. Although our understanding of the pathogenesis, clinical manifestations, and treatment of DPN have advanced greatly in recent years, further research is needed to expand our knowledge of the etiologies and pathogenesis of DPN and discover better methods to prevent the onset and progression of this disorder, independent of glucose control. Clinicians need to be vigilant when asking about neurologic symptoms and examining patients’ feet for the signs of DPN. Patients with proximal or unilateral findings should be referred for a full neurologic evaluation. For patients with DPN, improvement in control of glucose and attention to the other modifiable risk factors is essential to prevent or ameliorate morbidity. Neuropathic pain should be treated aggressively using drugs approved by the FDA for this condition. Ongoing foot examinations and referral of patients with high-risk feet to podiatrists is mandatory. DPN is a complication of diabetes that should never be “forgotten.”

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