

Management of Neuropathy and Foot Problems in Diabetic Patients

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Diabetic neuropathy (DN) is a complex set of clinical syndromes that affect distinct regions of the nervous system, either singly or combined. DN is the most common form of neuropathy in the developed countries of the world and is responsible for 50% to 75% of nontraumatic amputations. It is also the most life damaging—once autonomic neuropathy sets in, the mortality rate approximates 25% to 50% within 5 to 10 years. Distal symmetric polyneuropathy, the most common form of DN, usually involves both small and large nerve fiber damage. Small nerve fiber neuropathies occur early and are often present without objective signs or electrophysiologic evidence of nerve damage. The greatest risk is foot ulceration and subsequent gangrene. Large nerve fiber neuropathies, which involve the sensory and motor nerves, are generally neuropathies of signs rather than symptoms. Clinical presentation usually includes a “glove and stocking” distribution of sensory loss and the greatest risk is Charcot’s neuroarthropathy. Diagnosis of DN relies heavily on a careful patient history and physical examination. Most critical is that both the patient and the patient’s shoes should be examined and corrective measures taken. Several studies have shown that good diabetes control can significantly reduce neuropathy. As new drugs and ways to enhance nerve blood flow and block pain pathways at different levels are being explored, the effective treatment of DN and the reduction of its impact on quality of life as well as mortality will become a reality. Patient education and preventive strategies, however, are still the best ways to treat the complications of neuropathy and reduce the amputation rate.

Diabetic neuropathy (DN) is the most common and troublesome complication of diabetes mellitus, leading to great morbidity and mortality and resulting in a huge economic burden (1,2). DN is the most common form of neuropathy, accounting for more hospitalizations than all other diabetic complications combined, and is responsible for 50% to 75% of nontraumatic amputations (2,3). DN is a complex set of clinical syndromes that affect distinct regions of the nervous system either singly or combined. It may be silent and go undetected while executing its ravages, or it may present with clinical symptoms and signs that, although nonspecific, are insidious with slow progression, often mimicking symptoms of other diseases. DN is therefore diagnosed by exclusion.

KEY POINT

The major morbidity associated with somatic neuropathy is foot ulceration—the precursor of gangrene and limb loss. Each year ~85,000 amputations are performed on diabetic patients in the United States—1 every 10 minutes—and up to 75% are preventable!

The true prevalence is not known; reports vary from 10% to 90% in diabetic patients depending on the criteria and methods used to define neu-

ropathy. Neurologic complications occur equally in type 1 and type 2 diabetes and additionally in various forms of acquired diabetes (1–5). Of the 25% of patients attending a diabetes clinic who volunteered symptoms, 50% were found to have neuropathy after a simple clinical test such as the ankle jerk or vibration perception test; ~ 90% tested positive on sophisticated tests of autonomic function or peripheral sensation (6). The major morbidity associated with somatic neuropathy is foot ulceration, the precursor of gangrene and limb loss. Neuropathy increases the risk of amputation 1.7-fold; the risk increases to 12-fold if there is deformity (itself a consequence of neuropathy) and 36-fold if there is a history of ulceration (7). Each year 85,000 amputations are performed in the United States on diabetic patients—1 every 10 minutes—and neuropathy is the major contributor in 87% of these cases (1). It is also the most life damaging of the diabetic complications and has tremendous ramifications for the quality of life. Once autonomic neuropathy sets in, life can become quite dismal, and the mortality rate approximates 25% to 50% within 5 to 10 years (8,9).

CLASSIFICATION OF DN

DN is not a single entity but a number of different syndromes ranging from subclinical to clinical manifestations, depending on the classes of nerve fibers involved. According to the San Antonio Convention (10), the main groups of neurologic disturbance in diabetes include: (a) *subclinical neuropathy*, determined by abnormalities in electrodiagnostic and quantitative sensory testing; (b) *focal neuropathy or syndromes*; and (c) *diffuse clinical neuropathy* with distal symmetric sensorimotor and autonomic syndromes.

SUBCLINICAL NEUROPATHY

Subclinical neuropathy is diagnosed on the basis of: (a) abnormal electrodiagnostic tests with decreased nerve conduction velocity or decreased amplitudes; (b) abnormal quantitative sensory tests (QST) for vibration, tactile, and thermal warming and cooling thresholds; and (c) quantitative autonomic function tests (QAFT) revealing diminished heart rate variation with deep breathing, Valsalva maneuver, and postural testing. The different clinical presentations of diabetic neuropathy are sche-

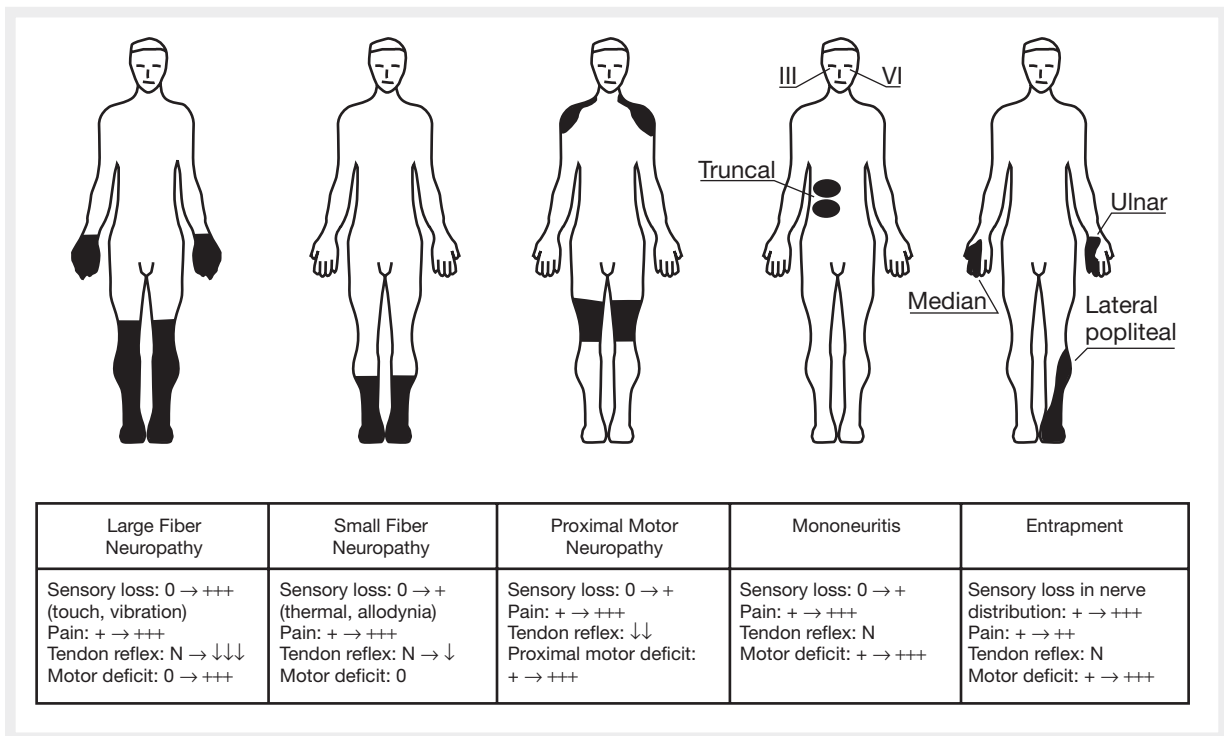


Figure 1. Clinical presentations of diabetic neuropathy. Reprinted with permission from Vinik AI, Park TS, Stansberry KB, Pittenger GL. Diabetic neuropathies. Diabetologia. 2000;43:957–973.

matically illustrated in **Figure 1**. (For further details see reference 11.)

FOCAL NEUROPATHY

Mononeuritis and Entrapment Syndromes

Mononeuropathies occur primarily in the older population; the onset is generally acute and associated with pain, and the course is self-limiting, resolving within 6 to 8 weeks. Mononeuropathies are due to vascular obstruction after which adjacent neuronal fascicles take over the function of those infarcted by the clot (6). They must be distinguished from entrapment syndromes that start slowly, progress, and persist without intervention (**Table I**).

Common entrapment sites in diabetic patients involve median, ulnar, radial nerves; femoral, lateral cutaneous nerves of the thigh; peroneal; and medial and lateral plantar nerves. Carpal tunnel syndrome occurs twice as frequently in people with diabetes compared with a normal, healthy population, and its increased prevalence in diabetes may be related to repeated undetected trauma, metabolic changes, or accumulation of fluid or edema within the confined space of the carpal tunnel (12). If recognized, the diagnosis can be confirmed by electrophysiologic study, and therapy is straightforward. The mainstays of nonsurgical treatment are resting the wrist aided by the placement of a wrist splint in a neutral position for day and night use; the addition of mild diuretic, antiinflammatory drug medications; and injections of local anesthetics and steroids in refractory cases. If medical treatment fails, however, surgical treatment is advisable and consists of sectioning the volar carpal ligament

(13). The decision to proceed with surgery should be based on several considerations, including severity of symptoms, appearance of motor weakness, and failure of nonsurgical treatment.

DIFFUSE CLINICAL NEUROPATHY

Diffuse neuropathies can be proximal or distal. For a discussion of the proximal neuropathies see reference 14. Distal symmetric polyneuropathy (DSPN), also known as distal symmetrical sensory polyneuropathy (DSSP), is the most common and widely recognized form of DN. Onset is usually insidious but occasionally acute following stress or initiation of therapy for diabetes. DSPN may be either sensory or motor and involves small fibers, large fibers, or both (15). **Figure 2** shows the usual clinical presentation of the large and small fiber neuropathies.

Small Fiber Neuropathies

Small nerve fiber dysfunction usually occurs early and often is present without objective signs or electrophysiologic evidence of nerve damage (16). It manifests early with symptoms of pain and hyperalgesia in the lower limbs, followed by a loss of thermal sensitivity and reduced light touch and pinprick sensation (12). Small fiber neuropathies can present in a variety of ways. Clinical manifestations include:

- Prominent symptoms. Pain is of the C-fiber type, burning and superficial and associated with allodynia, that is, interpretation of all stimuli (eg, touch) as painful;
- Hypoalgesia late in the condition;

TABLE I.

MONONEURITIS VERSUS ENTRAPMENT

<i>Mononeuritis</i>	<i>Entrapment</i>
<ul style="list-style-type: none"> ● Onset sudden ● Usually single nerve but may be multiple ● Common nerves: C3, C6, C7, ulnar, median, peroneal ● Not progressive and resolves ● Treatment: symptomatic 	<ul style="list-style-type: none"> ● Onset gradual ● Single nerves exposed to trauma ● Common nerves: median, ulnar, peroneal, medial and lateral plantar ● Progressive ● Treatment: rest, splints, diuretics, steroid injections, and surgery for paralysis

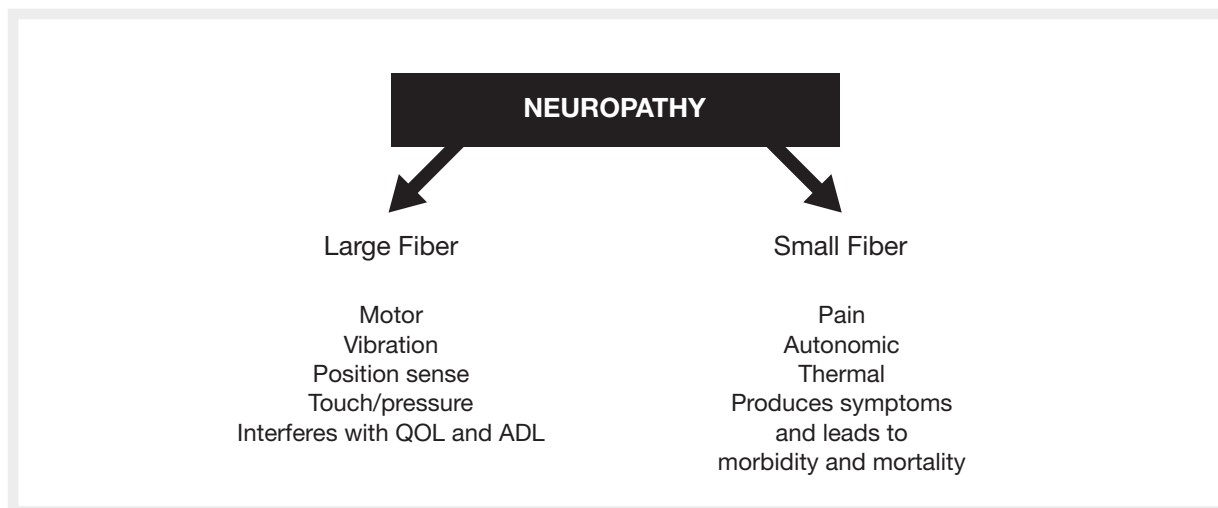


Figure 2. Distal symmetric polyneuropathy. ADL = activities of daily living; QOL = quality of life.

- Defective warm thermal sensation;
- Defective autonomic function with decreased sweating, dry skin, impaired vasomotion and blood flow, and a cold foot;
- Remarkable intactness of reflexes and motor strength;
- Electrophysiologic silence;
- Loss of cutaneous nerve fibers using PGP 9.5 staining;
- Clinical diagnosis by reduced sensitivity to 1.0-g Semmes-Weinstein monofilament and pricking sensation using the Waardenberg wheel or similar instrument; and
- Abnormalities in thresholds for warm thermal perception, neurovascular function, pain, and quantitative sudorimetry and quantitative autonomic function tests.

Risk: Foot ulceration and subsequent gangrene.

Acute painful neuropathy. Some patients develop a predominantly small fiber neuropathy that manifests with pain and paresthesia early in the course of diabetes. It may be associated and is often worsened with the initiation of therapy with insulin or sulfonylureas and has been termed *insulin neuritis* (17). By definition it has a duration of <6 months. Symptoms often are exacerbated at night and occur in the feet more than the hands. Spontaneous episodes of pain can be severely disabling, and the pain varies in intensity and character. In

some patients, the pain has been variably described as burning, lancinating, stabbing, or sharp. Paresthesia or episodes of distorted sensation, such as pins and needles, tingling, coldness, numbness, or burning, often accompany the pain (15). The lower legs may be exquisitely tender to the touch, with any disturbance of the hair follicles resulting in excruciating pain. Because pain can be aggravated by repeated contact of the lower limbs with foreign objects, even basic daily activities, such as sitting at a desk, may be disrupted.

This neuropathy may also be associated with profound weight loss and severe depression, which has been termed *diabetic neuropathic cachexia* (18). This syndrome occurs predominantly in male patients and may occur at any time in the course of both type 1 and type 2 diabetes. It is self-limiting and invariably responds to simple symptomatic treatment. Conditions such as Fabry's disease, amyloidosis, HIV infection, heavy metal poisoning (such as with arsenic), and excess alcohol consumption should be excluded. It does overlap with the idiopathic variety of acute painful small fiber neuropathy that is also a diagnosis by exclusion (19).

Chronic painful neuropathy. Far more common, however, is chronic painful polyneuropathy. With this neuropathy, onset of pain occurs often years later in the course of the diabetes, and the pain usually persists for >6 months and becomes debilitat-

ing. This condition may result in tolerance to narcotics and analgesics and finally addiction. It is extremely resistant to all forms of intervention and frustrating to both patient and physician.

The mechanism for pain in small fiber neuropathy is not well understood. Hyperglycemia may be a factor in lowering the pain threshold, and the condition may appear soon after initiation of therapy (17). A striking amelioration of symptoms with the intravenous administration of insulin can be achieved (20). There is a sequence in DN, beginning when nerve function (C-fiber and A β -function) is intact and there is no pain. With damage to C fibers there is sympathetic sensitization, and peripheral autonomic stimulation is interpreted as painful. With death of C fibers there is nociceptor sensitization and A β fibers, which conduct all varieties of peripheral stimuli (eg, touch), and these are interpreted as painful (eg, allodynia). In time there is reorganization at the cord level, and the patient experiences cold hyperalgesia. Ultimately, even with the death of all fibers pain is registered in the cerebral cortex whereupon the syndrome becomes chronic without the need for peripheral stimulation. Disappearance of pain may not necessarily reflect nerve recovery but rather nerve death. When patients volunteer the loss of pain, progression of the neuropathy must be excluded by careful examination.

Large Fiber Neuropathies

Large fiber neuropathies may involve either the sensory or the motor nerves or both and are usually neuropathies of signs rather than symptoms. Large fibers subservise motor function, vibration perception, position sense, and cold thermal perception. Unlike small nerve fibers, these are the myelinated, rapidly conducting fibers that begin in the toes and have their first synapse in the medulla oblongata. They tend to be affected because of their length and the tendency in diabetes for nerves to “die back.” Because they are myelinated, these are the fibers represented in electromyography, and subclinical abnormalities in nerve function are readily detected. Symptoms may be minimal: sensation of walking on cotton, floors feeling “strange,” inability to turn the pages of a book, or inability to discriminate

among coins. The clinical presentation of large fiber neuropathies may include:

- Impaired vibration perception (often the first objective evidence) and position sense;
- Depressed tendon reflexes;
- A δ -type, deep-seated gnawing pain, dull like a toothache in the bones of the feet, or a crushing or cramplike pain;
- Sensory ataxia (waddling like a duck);
- Wasting of small muscles of feet with hammer-toes (intrinsic minus foot and hands) with weakness of hands and feet;
- Shortening of the Achilles tendon with pes equinus; and
- Increased blood flow (hot foot).

Risk: Charcot’s neuroarthropathy.

Most patients with DSPN have a mixed variety of neuropathy with both large and small nerve fiber damage. A “glove and stocking” distribution of sensory loss is almost universal (21). Early in the course of the neuropathic process, multifocal sensory loss also might be found. In some patients, severe distal muscle weakness can accompany the sensory loss, resulting in an inability to stand on the toes or heels.

DIFFERENTIAL DIAGNOSIS OF DN

The diagnosis of DN (**Table II**) relies heavily on a careful patient history and physical examination for which a number of tools have been developed by Young et al (4), Dyck (22), Vinik and Mitchell (23), and others (24,25). The initial neurologic evaluation should be directed to the detection of the specific part of the nervous system affected by diabetes (**Figure 1**).

Diagnostic strategies for neuropathy include:

- Comprehensive foot examination. **Patients should not be examined with their shoes on. Examine both the patient and the shoes!** Assess the patient’s skin integrity, especially between the toes and under the metatarsal heads; presence of hair; muscle wasting (especially interosseus with intrinsic minus foot); hammertoe or other deformities; biomechanics; calluses; ulceration; infections; nail hygiene; and circulation. Obtain a history of claudication and assess pedal pulses.

TABLE II.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF NEUROPATHY

<i>Congenital/Familial</i>	<i>Charcot-Marie-Tooth Atrophy</i>
Traumatic	Entrapment syndromes
Inflammatory	Sarcoidosis Leprosy Lyme disease HIV infection
Neoplastic	Carcinoma, paraneoplastic syndromes Myeloma, amyloidosis Reticuloses, leukemias, lymphomas
Metabolic/Endocrine	Diabetes mellitus Uremia Pernicious anemia (B ₁₂ deficiency) Hypothyroidism Porphyria (acute intermittent)
Vascular	Diabetes, vasculitis
Toxic	Alcohol Heavy metals (lead, mercury, arsenic) Hydrocarbons, chemotherapeutic drugs
Autoimmune	Diabetes Phospholipid antibody (PLA) syndrome Chronic inflammatory demyelinating neuropathy Multifocal motor neuropathy Guillain-Barré syndrome

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If in doubt, check ankle-brachial indices of blood pressure.

- Footwear examination. Examine the patient's shoes for quality, supports, inserts, and content. With loss of pain perception, all kinds of foreign objects may be found in the shoes.
- Physical examination. Test the patient for muscle strength, reflexes, and sensitivity to vibration; pressure perception using 1-g and 10-g monofilaments; and warm and cold temperature and touch perception at initial visit and then at least once a year and more frequently if ulcers occur.
- Nerve conduction studies. Recommended to evaluate nerve conduction electricity at the clinician's discretion as symptoms dictate; especially valuable to diagnose entrapment neuropathies but do not provide any discriminating value for etiology.
- Electromyography. To determine how well muscles respond to electrical signals from nearby nerves. This study is often set up concurrently

with nerve conduction studies. Valuable in distinguishing inflammatory demyelinating conditions and nerve root involvement.

- Heart rate variability. To assess the heart's response to deep breathing and changes in blood pressure and posture. Important for evaluating autonomic nervous system function and predicting outcome.
- Blood flow. To evaluate the status of blood flow to the skin. Important for predicting foot ulceration or the danger of Charcot's neuroarthropathy and response to intervention.

A bedside neurologic examination is quick and easy but provides nominal or ordinal measures and contains substantial inter- and intraindividual variation. For example, it is useless to measure vibration perception with a tuning fork other than one that has a frequency of 128 Hz. Similarly, a 10-g monofilament is good for predicting foot ulceration as is the Achilles reflex. However, both

are insensitive to the early detection of neuropathy; a 1.0-g monofilament increases the sensitivity from 60% to 90% (26). To find entrapment syndromes, sensory function must be evaluated on both sides of the feet and hands. Tinel's sign is not only useful for carpal tunnel problems but can be applied to the ulnar notch, head of the fibula, and below the medial tibial epicondyle for ulnar, peroneal, and medial plantar entrapments, respectively. The 1988 San Antonio conference on DN and the 1992 conference of the American Academy of Neurology (10) recommended that at least 1 parameter from each of the following 5 categories be measured to classify DN: (a) symptom profiles, (b) neurologic examination, (c) QST, (d) nerve conduction study, and (e) autonomic function testing. The least reliable measure is the Neurologic Symptom Score. The QST and QAFT are objective indices of neurologic functional status. Combined, these tests cover vibratory, proprioceptive, tactile, pain, thermal, and autonomic function. Recently, the development of a number of relatively inexpensive devices has allowed the suitable assessment of somatosensory function, including vibration, thermal, light-touch, and pain perception (27). These instruments can assess cutaneous sensory functions noninvasively, and their measurements are correlated with specific neural fiber function.

QAFT consists of a series of simple, noninvasive tests for detecting cardiovascular autonomic neuropathy (16,28). These tests are based on detection of heart rate and blood pressure response to a series of maneuvers. Specific tests are used to evaluate disordered regulation of gastrointestinal, genitourinary, and pseudomotor function and peripheral skin blood flow induced by autonomic DN (26).

Biopsy of nerve tissue may be helpful for excluding other causes of neuropathy and in the determination of predominant pathologic changes in patients with complex clinical findings as a means of dictating choice of treatment (29,30). Skin biopsy has some clinical advantages in the diagnosis of small fiber neuropathies by quantification of PGP 9.5 when all other measures are negative (31,32). Diabetes as the cause of neuropathy is diagnosed by exclusion of various other causes of neuropathy (12,33).

TREATING DN

The treatment of DN, as with most complications of diabetes, begins with overall metabolic—and particularly glycemic—control. For example, the Diabetes Control and Complications Trial (DCCT) (34) showed that the difference in mean hemoglobin A_{1c} between treatment groups (7% versus 9%) slowed the onset and progression of neuropathy by ~60% in patients with type 1 disease. Once neuropathy is diagnosed, therapy can then be instituted with the goal of both ameliorating symptoms and preventing its progression. Successful management of these syndromes must be geared to the individual pathogenic processes.

KEY POINT

The DCCT research group reported significant effects of intensive insulin therapy on the prevention of neuropathy. Prevalence rates for clinical or electrophysiologic evidence of neuropathy were reduced by 50% in patients treated by intensive insulin therapy over a 5-year period.

MANAGEMENT OF PATHOGENIC MECHANISMS

Control of Hyperglycemia

Retrospective and prospective studies have suggested a relationship between hyperglycemia and the development and severity of DN. Pirart (35) followed 4400 diabetic patients over 25 years and showed an increase in prevalence of clinically detectable DN from 12% of patients at the time of diagnosis of diabetes to almost 50% after 25 years. The highest prevalence occurred in those people with the poorest diabetes control. The DCCT research group (34) reported significant effects of intensive insulin therapy on prevention of neuropathy. The prevalence rates for clinical or electrophysiologic evidence of neuropathy were reduced by 50% in those treated by intensive insulin therapy over a 5-year period. At that stage of the study, only 3% of the patients in the primary prevention

cohort treated by intensive insulin therapy showed minimal signs of DN as compared with 10% of those treated by the conventional regimen. In the secondary prevention cohort, intensive insulin therapy significantly reduced the prevalence of clinical neuropathy by 56% (7% in the intensive insulin therapy group versus 16% in the conventional therapy group).

Results of the DCCT support the necessity for strict glycemic control, but the effect of insulin as a growth factor and immunomodulator, aside from its metabolic effects, must also be investigated. In the United Kingdom Prospective Diabetes Study (UKPDS), control of blood glucose was associated with improvement in vibration perception (36–38). In the more recent Steno trial (39), a reduction of the odds ratio to 0.32 was reported for the development of autonomic neuropathy. This stepwise, progressive study involved the treatment of type 2 diabetes patients with hypotensive drugs, including angiotensin-converting enzyme inhibitors, calcium channel antagonists, hypoglycemic agents, aspirin, hypolipidemic agents, and antioxidants. The findings argue strongly for the multifactorial nature of neuropathy and the need to address the multiple metabolic abnormalities.

α -Lipoic acid* Lipoic acid (1,2-dithiolane-3-pentanoic acid), a derivative of octanoic acid, is present in food and is also synthesized by the liver. It is a natural cofactor in the pyruvate dehydrogenase complex where it binds acyl groups and transfers them from one part of the complex to another. α -Lipoic acid, also known as thioctic acid, has generated considerable interest as a thiol-replenishing and redox-modulating agent and has been shown to be effective in ameliorating both the somatic and autonomic neuropathies in diabetes (40–42). It is currently undergoing extensive trials in the United States as both an antidiabetic agent and for the treatment of DN.

γ -Linolenic acid. Linoleic acid, an essential fatty acid, is metabolized to dihomo- γ -linolenic acid, which serves as an important constituent of neu-

ronal membrane phospholipids and as a substrate for prostaglandin E formation, seemingly important for preservation of nerve blood flow. In diabetes, conversion of linoleic acid to γ -linolenic acid (GLA) and subsequent metabolites is impaired, possibly contributing to the pathogenesis of DN (43). A recent multicenter, double-blind, placebo-controlled trial using GLA for 1 year demonstrated significant improvements in both clinical measures and electrophysiologic testing (44).

Human intravenous immunoglobulin. Immune intervention with human intravenous immunoglobulin (IVIg) has become appropriate in some patients with forms of peripheral DN that are associated with signs of antineuronal autoimmunity (45,46). Treatment with IVIg is well tolerated and is considered safe, especially with respect to viral transmission (47). The major toxicity of IVIg has been an anaphylactic reaction, but the frequency of these reactions is now low and confined mainly to patients with immunoglobulin (usually IgA) deficiency. Patients may experience a severe headache due to aseptic meningitis, which resolves spontaneously. In some instances, it may be necessary to combine treatment with prednisone or azathioprine, or both. Relapses may occur, requiring repeated courses of therapy.

MANAGEMENT OF PAIN

Management of pain constitutes one of the most difficult treatment issues in DN. Simple measures should be tried first. If no distinction is made for pain syndromes, then the numbers needed to treat to reduce pain by 50% are 1.4 for optimal dose tricyclic antidepressants*, 1.9 for dextromethorphan*, 3.3 for carbamazepine*, 3.4 for tramadol, 3.7 for gabapentin*, 5.9 for capsaicin*, 6.7 for selective serotonin reuptake inhibitors*, and 10.0 for mexiletine* (48). If, however, pain is divided according to its derivation from nerve fiber type (A δ , C fiber), spinal, cord, or cortical, then different types of pain will respond to different therapies as described below.

* Not FDA-approved for the treatment of DN.

* Not FDA-approved for symptomatic management of DN.

C-Fiber Pain

Initially when there is ongoing damage to the nerves, a patient experiences pain of the burning, lancinating, dysesthetic type, often accompanied by hyperalgesia and allodynia. Because the peripheral sympathetic nerve fibers are also small unmyelinated C fibers, sympathetic blocking agents (eg, clonidine) may lessen the pain. Loss of sympathetic regulation of sweat glands and arteriovenous shunt vessels in the foot creates a favorable environment for bacteria to penetrate and multiply. These fibers utilize the neuropeptide substance P as their neurotransmitter, and depletion of axonal substance P (eg, by using capsaicin) will often lead to amelioration of pain. However, when the destructive forces persist, the individual becomes pain free and develops impaired warm temperature and pain thresholds. Therefore, disappearance of pain in these circumstances should be hailed as a warning that the neuropathy is progressing.

Capsaicin. Capsaicin is extracted from chili peppers. A simple, inexpensive treatment can be made by adding 1 to 3 teaspoons of cayenne pepper to a jar of cold cream and applying the mixture to the area of pain. Capsaicin has high selectivity for a subset of sensory neurons, which have been identified as unmyelinated C fiber afferent or thin-myelinated ($A\delta$) fibers. Prolonged application of capsaicin depletes stores of substance P and possibly other neurotransmitters from sensory nerve endings, which reduces or abolishes the transmission of painful stimuli from the peripheral nerve fibers to the higher centers (49). Care must be taken to avoid the eyes and genitals, and gloves must be worn. Because of capsaicin's volatility, it is safer to cover affected areas with plastic wrap. Initial exacerbation of symptoms is followed by relief in 2 to 3 weeks.

Clonidine. There is an element of sympathetic-mediated C fiber-type pain that can be overcome with clonidine (α_2 -adrenergic agonist) or phentolamine*. Clonidine can be applied topically (50), but the dose titration may be more difficult. If

clonidine fails, the local anesthetic agent mexiletine warrants a trial.

$A\delta$ -Fiber Pain

$A\delta$ -fiber pain is a more deep-seated, dull, gnawing ache, which often does not respond to the previously described measures. A number of different agents have been used for the pain associated with these fibers with varying success.

Insulin. Continuous intravenous insulin infusion without resort to blood glucose lowering may be useful in these patients. A response with reduction of pain usually occurs within 48 hours (20), and the insulin infusion can be discontinued. If this measure fails, there are several other medications available that may abolish the pain.

Nerve-blocking agents. Lidocaine given by slow infusion has been shown to provide relief of intractable pain for 3 to 21 days. This form of therapy may be of most use in self-limited forms of neuropathy. If successful, therapy can be continued with oral mexiletine. These compounds target the pain caused by hyperexcitability of superficial, free nerve endings (51).

Tramadol and dextromethorphan. There are 2 possible therapies. Tramadol is a centrally acting analgesic for treating moderate to severe pain, and it has recently been reported to provide pain relief in DN (52). Another spinal cord target for pain relief is the excitatory glutamergic N-methyl-D-aspartate (NMDA) receptor. Blockade of NMDA receptors is believed to be one mechanism by which dextromethorphan exerts analgesic efficacy (53). An accomplished pharmacist can provide a sugar-free solution of dextromethorphan.

Antidepressants. Clinical trials have focused on interrupting pain transmission using antidepressant drugs that inhibit the reuptake of norepinephrine or serotonin. This central action accentuates the effects of these neurotransmitters in activation of endogenous pain-inhibitory systems in the brain that modulate pain-transmission cells in the spinal cord (54). Side effects, including dysautonomia

* Not FDA-approved for symptomatic management of DN.

and dry mouth, can be troublesome with antidepressants and different ones should be tried. Nortriptyline*, for example, may lessen some of the anticholinergic effects of amitriptyline*.

Carbamazepine. Several double-blind, placebo-controlled studies have demonstrated carbamazepine to be effective in the management of pain in DN (12). Toxic side effects may limit its use in some patients; however, it is very useful for those patients with lightning or shooting pain.

Phenytoin*. Phenytoin (5,5-diphenylhydantoin) has long been used in the treatment of painful neuropathies. Double-blind crossover studies do not demonstrate a therapeutic benefit of phenytoin compared with placebo in DN (55), and side effects mitigate its use in people with diabetes. Its ability to suppress insulin secretion has resulted in precipitation of hyperosmolar diabetic coma.

Gabapentin. Gabapentin is an effective anticonvulsant whose mechanism is not well understood, yet it holds promise as an analgesic agent in painful neuropathy (56). In a multicenter study conducted in the United States (57), gabapentin monotherapy appeared to be efficacious for treating pain and sleep interference associated with diabetic peripheral neuropathy. It also exhibits positive effects on mood and quality of life (58).

Transcutaneous nerve stimulation (electrotherapy). Transcutaneous nerve stimulation (electrotherapy) occasionally may be helpful and certainly represents one of the more benign therapies for painful neuropathy (59). Care should be taken to move the electrodes around to identify sensitive areas and obtain maximal relief.

Analgesics. Analgesics are rarely of benefit in treating painful neuropathy, although they may be useful on a short-term basis for treating self-limited syndromes such as painful diabetic third-nerve palsy. Generally, the use of narcotics for chronic pain should be avoided because of the risk of addiction.

Calcitonin*. In a placebo-controlled study, 10 patients with painful DN were treated with 100 IU of calcitonin per day. About 39% of patients had near-complete relief of symptoms, and improvement was seen after only 2 weeks of treatment (60).

MANAGEMENT OF SMALL FIBER NEUROPATHIES

The following management guidelines are essential:

- Patients must be instructed on foot care and a daily foot inspection.
- Patients should have a mirror in the bathroom for inspecting the soles of their feet.
- Patients must be provided with a monofilament since self-testing reduces ulcers.
- Patients should wear padded socks.
- Shoes must fit well with adequate support and must be inspected daily for the presence of any foreign bodies (eg, nails, pins).
- Patients must exercise care about exposure to heat (eg, no falling asleep in front of fires).
- Emollient creams should be used for the drying and cracking of skin.
- After bathing, feet should be thoroughly dried and powdered between the toes.
- Nails should be cut transversely, preferably by a podiatrist.

MANAGEMENT OF LARGE FIBER NEUROPATHIES

Patients with large fiber neuropathies are incoordinated and ataxic. As a result, they are more likely to fall than non-neuropathic, age-matched patients (61). It has recently been demonstrated that high-intensity strength training in older persons increases muscle strength in a variety of muscles. More importantly, strength training resulted in improved coordination and balance, quantifiable with backward tandem walking (62). Thus, it is vital to embark on a program of strength training and improvement of balance. The following management options should be considered:

- Gait and strength training;

* Not FDA-approved for symptomatic management of DN.

- Fitted orthotics with proper shoes for any deformities;
- Tendon lengthening for Achilles tendon shortening;
- Bisphosphonates for osteopenia;
- Surgical reconstruction and full-length casting as necessary; and
- Pain management.

PREVENTION AND TREATMENT OF FOOT PROBLEMS

About 85,000 amputations—half the national total—are performed each year on diabetic patients due to peripheral neuropathy, and up to 75% of these could be prevented with better foot care (63,64). Physicians must adequately assess the diabetic patient’s risk for ulcers and amputations.

Table III outlines factors that increase those risks.

Foot Examination

Physicians should perform a comprehensive foot examination at least annually; those with more risk factors or a history of ulceration should have their feet checked more often, including a visual inspection at every office visit. Perhaps the single most effective means to prevent foot problems leading to ulceration is patient education.

Patient Education

The following guidelines should decrease ulcer risk and incidence:

- Patients with neuropathy or evidence of increased plantar pressure (measured or suggested by exam) should wear well-fitted walking or athletic shoes, which can cut ulceration rates in half.
- Some patients, especially those with bony deformities, may need custom shoes to redistribute pressure.
- Physicians should treat minor skin problems (eg, dryness or tinea pedis) promptly to prevent progression to ulceration.
- Patients with symptoms of claudication should receive further vascular assessment (65,66).

Patient education should focus on:

- Glycemic control;
- Blood pressure and lipid control;
- Smoking cessation;
- Understanding the loss of protective sensation;
- Daily foot monitoring and proper care; and
- Appropriate footwear (65,66).

Patients should be instructed as follows for self-care:

- Clean—but don’t soak—feet daily with warm water and mild soap. Dry feet thoroughly, especially between toes.
- Inspect feet daily for cuts, blisters, swelling, calluses, or infection. Use a mirror if necessary to inspect the soles.

TABLE III. RISK FACTORS FOR DIABETIC FOOT ULCERS AND AMPUTATION	
<i>General Risk Factors</i>	<i>Foot-Specific Risk Factors</i>
<ul style="list-style-type: none"> ● Diabetes duration >10 years ● Male sex ● Poor glycemic control ● Cardiovascular, retinal, or renal complications 	<ul style="list-style-type: none"> ● Peripheral neuropathy ● Altered biomechanics (in the presence of neuropathy) <ul style="list-style-type: none"> – Evidence of increased pressure (eg, erythema, hemorrhage under a callus) – Bony deformity ● Peripheral vascular disease (decreased or absent pedal pulse) ● History of ulcers or amputation ● Severe nail pathology

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- Use moisturizing lotion but avoid getting it between the toes.
- After a bath or shower, file corns and calluses gently with a pumice stone.
- Weekly, or as needed, cut toenails to the shape of the toes and file.
- Always wear shoes or slippers.
- Wear well-fitting, appropriate shoes and break them in gradually. Before putting shoes on, check for rough seams, sharp edges, or objects that could hurt the feet.
- See a podiatrist when indicated (63).

In the primary-care setting, the decision pathway outlined in **Table IV** provides a conve-

nient framework for evaluation and treatment decisions. Once an ulcer occurs, it is best to refer the patient to a specialist in the treatment of diabetic foot ulcers.

DIABETIC NEUROPATHIES AND FOOT CARE: PROSPECTS FOR THE FUTURE

Management of DN and prevention of associated foot problems encompass a wide variety of therapies. Treatment must be individualized in a manner that addresses the particular manifestation or underlying pathogenesis of each patient’s unique clinical presentation without subjecting the patient to untoward medication effects. New ways to

TABLE IV. DIABETIC FOOT ASSESSMENT AND TREATMENT GUIDELINE	
Assessment Category	Goal/Management
<p>Category 0</p> <ul style="list-style-type: none"> ● Sensate to 10-g SWF ● No deformities ● Intact pulses ● No prior ulcer or LEA <p>Category 1</p> <ul style="list-style-type: none"> ● Insensate to 10-g SWF ● No deformities ● Pulse present ● No prior ulcer or LEA <p>Category 2</p> <ul style="list-style-type: none"> ● Insensate to 10-g SWF ● Deformities and/or absent pulse ● No prior ulcer or LEA <p>Category 3</p> <ul style="list-style-type: none"> ● Prior ulceration or amputation 	<p>Low Risk <i>Goal:</i></p> <ul style="list-style-type: none"> ● Risk-factor prevention <p><i>Management:</i></p> <ul style="list-style-type: none"> ● Glycemic, blood pressure, and lipid control ● Self-care education ● Annual foot exam ● Any change in status, reclassify <p>Moderate Risk <i>Goal:</i></p> <ul style="list-style-type: none"> ● Ulcer prevention <p><i>Management:</i></p> <ul style="list-style-type: none"> ● Standard protective footwear ● Self-care education ● Palliative podiatry care ● Reevaluate at 4–6 months ● Any change in status, reclassify <p>High Risk <i>Goal:</i></p> <ul style="list-style-type: none"> ● Ulcer prevention <p><i>Management:</i></p> <ul style="list-style-type: none"> ● Extra-depth or custom shoe ● Self-care education ● Palliative podiatry care ● Vascular assessment if critical ischemia ● Reevaluate in 2–3 months ● Any change in status, reclassify <p>Very High Risk <i>Goal:</i></p> <ul style="list-style-type: none"> ● Re-ulceration prevention <p><i>Management:</i></p> <ul style="list-style-type: none"> ● Same as high risk, but reevaluate in 1–2 months

LEA = lower-extremity amputation; SWF = Semmes-Weinstein filament. Adapted with permission from Rith-Najarian S, Reiber G. Prevention of foot problems in persons with diabetes. *J Fam Pract.* 2000;49:S30–S39; Adapted with permission from Vinik A, Pittenger G, Stansberry K, et al. Neurotrophic factors. In: *Textbook of Diabetic Neuropathy*. Stuttgart, Germany: Georg Thiem Verlag; 2003:129–169.

enhance blood flow to nerves via vasa nervorum are being explored, such as the prostacyclin analogue beraprost*; blockade of the vasoconstrictors endothelin, angiotensin, and thromboxane A₂; and drugs that normalize abnormalities in metabolism, including Na/K-ATPase activity such as cilostazol, a potent phosphodiesterase inhibitor, and α -lipoic acid, a potent antioxidant, as well as drugs that combat nitrative stress. Prospects for amelioration of diabetic neuropathies are not as grim as once perceived. New and exciting agents that block pain pathways at different levels and more potent and less toxic aldose reductase inhibitors are in the research pipeline. Inhibition of protein kinase C has seen success in early phase 2 trials and has entered into phase 3 studies, and perhaps this therapy will appear in the clinic in the not-too-distant future.

SUMMARY

DN is a common complication of diabetes, often associated with considerable morbidity and mortality. The recent resurgence of interest in the vascular hypothesis, oxidative and nitrative stress, the neurotrophic hypothesis, and the possibility of the role of autoimmunity have opened up new avenues of investigation for therapeutic intervention. Paralleling our increased understanding of the causes of DN and the introduction of pathogenesis-based treatments have been refinements in our ability to measure quantitatively the different types of defects that occur in this disorder so that appropriate therapies can be targeted to specific fiber types. We now have a therapeutic armamentarium capable of mitigating the symptoms, but a more salutary approach is the introduction of new drugs aimed at the underlying pathogenesis and thereby the prevention of evolution of neuropathy to ulceration and gangrene with amputation.

The nationwide Healthy People 2000 initiative aims for a 50% reduction in the amputation rate, and this is best achieved with patient education and preventive strategies. The appearance of a foot ulcer should not be hailed as the time to start therapy but as a failure of the health care provider

to appropriately educate and monitor the patient. Fortunately, we also have powerful tools to recognize and treat the complications of neuropathy so that the goal of reducing its impact on activities of daily living and quality of life as well as mortality can be realized.

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Dialogue Box

EDITORIAL BOARD

What is responsible for the high mortality rate seen in patients with autonomic neuropathy?

VINIK

The high mortality rate stems from a number of things. First, from an epidemiologic perspective, autonomic neuropathy co-segregates with a number of known macrovascular disease risk factors, including hypertension, dyslipidemia, obesity, and elevated serum fibrinogen and type 1 plasminogen activated inhibitor levels. Thus, once autonomic neuropathy is found, the likelihood of death from a macrovascular event is increased. Second, for still unexplained reasons, patients with autonomic nerve dysfunction tend to be “non-dippers,” ie, their blood pressure doesn’t go down in the evening when they go to bed and assume a recumbent position. As a result, their blood pressure is higher, which increases their risk for developing progressive renal insufficiency and dying of kidney failure. Finally, life-threatening events can arise as a consequence of impaired autonomic function. Examples include aspiration as a result of gastroparesis, cardiac dysrhythmia with sudden death syndrome, and painless myocardial infarction resulting in the patient not seeking needed medical attention. Other examples include complications arising from foot ulcerations and amputation as a result of the loss of vascular reactivity blood flow to the skin and subcutaneous tissue, and complications resulting from the loss of the hypoxic respiratory drive during the perioperative period.

EDITORIAL BOARD

How do you manage the patient with autonomic neuropathy who presents with the combination of hypertension when supine and symptomatic orthostatic hypotension?

VINIK

Having patients sleep with their head elevated is a strategy commonly used in an effort to lower blood pressure when the patient is supine. Another strategy is to make use of an interesting paradox seen in this type of patient. Since the autonomic nerve dysfunction is a postganglionic lesion, you can drop the blood pressure centrally and at the same time increase the vasoconstrictive response so that you don’t get orthostasis by starting the patient on a centrally active α -2 adrenergic agonist such as clonidine. What it will do is cause central hypothalamic deafferentation that will drop the blood pressure during the day. Paradoxically, the drop in blood pressure seen when the patient goes from a supine to an erect position also improves, thus, you end up with a reduction in orthostasis plus a reduction in daytime blood pressure. It’s a very nice trick, but you have to be careful. You need to start with a tiny dose, such as 0.1 mg at night and slowly titrate it up, as needed, in 0.1-mg increments to a maximum dose of 0.4 to 0.5 mg/d. Another strategy that has been helpful is to use a somatostatin analog in tiny doses—0.05 to 0.1 μ g/kg. Although somatostatin has no impact on the hypertension that you would treat normally, it will help with the orthostasis since it prevents pooling of blood in the gastrointestinal tract (by causing vasoconstriction in the splanchnic bed), which in turn will drive more blood into the systemic circulation.

EDITORIAL BOARD

How do patients with pure small fiber pain present and how are they best managed?

VINIK

These patients typically present with a superficial, burning sensation (often described as “acidic”) involving their feet. Patients presenting with “burning feet” are best managed initially with an

Dialogue Box

agent like capsaicin that depletes axonal substance P. Since adrenergic activation also plays a role in the generation of small fiber pain, the use of a sympathetic blocking agent such as clonidine can also be used to lessen the pain. These 2 strategies should be your starting point.

EDITORIAL BOARD

Where do tricyclic antidepressants fit in your drug armamentarium for neuropathic pain?

VINIK

Tricyclics are actually the very last drugs in my treatment armamentarium. They certainly are not what I like to use in people who have autonomic nerve dysfunction.

EDITORIAL BOARD

How do patients with pain arising from large fiber neuropathy describe their pain?

VINIK

These patients typically complain that they have “concrete” in their feet. They may also complain of a dull ache, as if they had a “toothache” in their feet. Others complain of a dull gnawing in the bones of their feet.

EDITORIAL BOARD

What is your treatment strategy in these patients?

VINIK

I initially try to block the syndrome with subcutaneous insulin or intravenous insulin infusion. Usually within 24 to 48 hours, if the syndrome blocks, it blocks beautifully and you avoid having to administer major pain therapy. If that doesn't work, you can address the problem at the nerve transmission level working at the sodium pump, or at the spinal cord level, or you can address it more

centrally. I like to start with benign drugs, such as the ones that affect the GABA (γ -aminobutyric acid) pathway. Although gabapentin* (Neurontin[®]) is not FDA approved for diabetic neuropathy, it is used for diabetes. I also like to use dextromethorphan*, an NMDA receptor antagonist. It is available as DexAlone[®]* but it also comes in a cough mixture. Antiepileptic agents also work fairly well. I generally favor the newer antiepileptic agents such as Topamax[®] and lamotrigine*. Topamax is very effective used the right way, but it is not an easy drug to use. Further down on my list is tramadol.* I have not been enchanted by the selective serotonin reuptake inhibitors, which have not been shown to be particularly effective. Lastly, you get to drugs like nortriptyline* (not amitriptyline*). Provided your patient doesn't mind blurred vision, a dry tongue, and severe constipation, it would be one of my last options.

EDITORIAL BOARD

What about patients with “electrical” shooting pains?

VINIK

Electrical shooting pains are a different kettle of fish. Then you need to use the antiepileptic drugs.

EDITORIAL BOARD

Intact sensation to the 10-gram monofilament plays an important role in your foot classification system. Where do you get these filaments?

VINIK

The easiest thing to do is to buy 25 pounds of fishing line for \$5, cut it into inches, and make your own monofilaments. In my clinic we keep these strips in an ice cream cup and encourage

*Not FDA approved for treatment of diabetic neuropathy.

Dialogue Box

patients to take them home. We tell them there is magic in them and to test the strips themselves. What patients end up doing when they perform the test is inspect their own feet every day. I look at it as a form of behavioral therapy. Using this strategy, I have not seen a foot ulcer in about 10 years and I have not referred a single patient for debridement.

EDITORIAL BOARD

Do you treat onychomycosis to reduce the risk for maceration due to tinea pedis and a possible increased risk for infection?

VINIK

I treat onychomycosis but not for that particular reason. A great predictor of foot problems in diabetic patients is the presence of foot deformities, ie, if they have calluses or fungal nails, they end up squashing their feet into a shoe, applying uneven pressure to some spot or other. Thus, I am fairly aggressive about treating onychomycosis. I use 3 podiatrists who trim the nails and I place

many patients on ketoconazole. I treat them for 10 days a month for 6 months in an effort to clear up those nails. My goal is to prevent the nail from producing any distortion that could lead to ulceration.

EDITORIAL BOARD

What role do you see for aldose reductase inhibitors in the future?

VINIK

These agents have been around for more than 30 years and have always been viewed as holding great promise. Unfortunately, the agents studied to date have been found to be either too toxic, as was the case with sorbinil, or ineffective, like Statil, which never actually got into the nerves. Only one new aldose reductase inhibitor has the potential for rescuing that field of endeavor and it's not yet available.

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