

Diabetic Neuropathies: New Treatment Modalities

Therapies recently approved and on the horizon may stimulate nerve regeneration

BY AARON I. VINIK, MD, PhD

The clinical impact of diabetic neuropathies is multifactorial.¹ Diabetic neuropathy leads to both painful symptoms and neuropathic deficits. These in turn can cause impairment, disability and even handicaps, from complications such as foot ulcers, infections and Charcot neuroarthropathy. Diabetic foot ulcers have a major impact on mortality rates among diabetic patients and put a large burden on our health care system. The worst-case scenario, of course, is amputation. All of the aforementioned conditions negatively affect the patient's quality of life (Figure 1).

What is neglected, however, is the impact of larger-fiber neuropathy on physical functioning and stability, which is associated with depression and impaired activities of daily living and increasing the likelihood of falling by 15-fold. The cause of fractures in diabetes is not osteopenia but neuropathy.

Neuronal damage, from most insults and chronic disorders, involves multiple pathological processes and pathways. The disease initiation and progression of neuropathy begins with genetics. Factors such as apolipoprotein E4, aldose reductase Z2 alleles, angiotensin-converting enzyme polymorphism and the Toll-like receptor polymorphism confer and increase or decrease susceptibility to neuropathy in the presence of poor diabetes control.

These genetic factors are accompanied by a prodromal period in which there is inflammation. Inflammation coupled with oxidative and nitrosative stress, and protein kinase-C, selectins, vascular cell adhesion molecules, interleukin 6, tumor necrosis factor alpha, necrosis factor kappa-B, reactive oxygen species and nitrotyrosines all play a part.

These inflammatory and genetic characteristics inter-

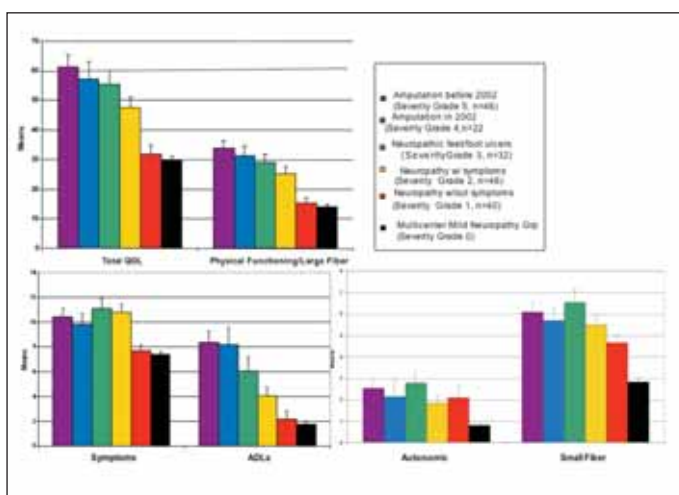


Figure 1. The Impact of neuropathy on the quality of life is significant. (Data from Vinik EJ, et al. *Diabetes Technol Ther.* 2005;7:497-508.)

act with an initiating event. During the course of months or years, glycation results in neuronal injury through the formation of advanced glycation end products. This process leads to epigenetic disorders, through the formation of poly (ADP-ribose) polymerases, resulting in a cycle of functional changes and progressive pathological changes (Figure 2).

DIAGNOSING DIABETIC NEUROPATHY

Diagnostic criteria. Neuropathy may be either asymptomatic or symptomatic. The presence of neuropathy must be confirmed by physical examination and at least two abnormalities should be present, including an abnormal neurological examination and at least one of the objective measures of nerve conduction, quantitative sensory, autonomic and motor function. No measure is specific for diabetic neuropathy, however, which requires the exclusion of other forms of neuropathy.

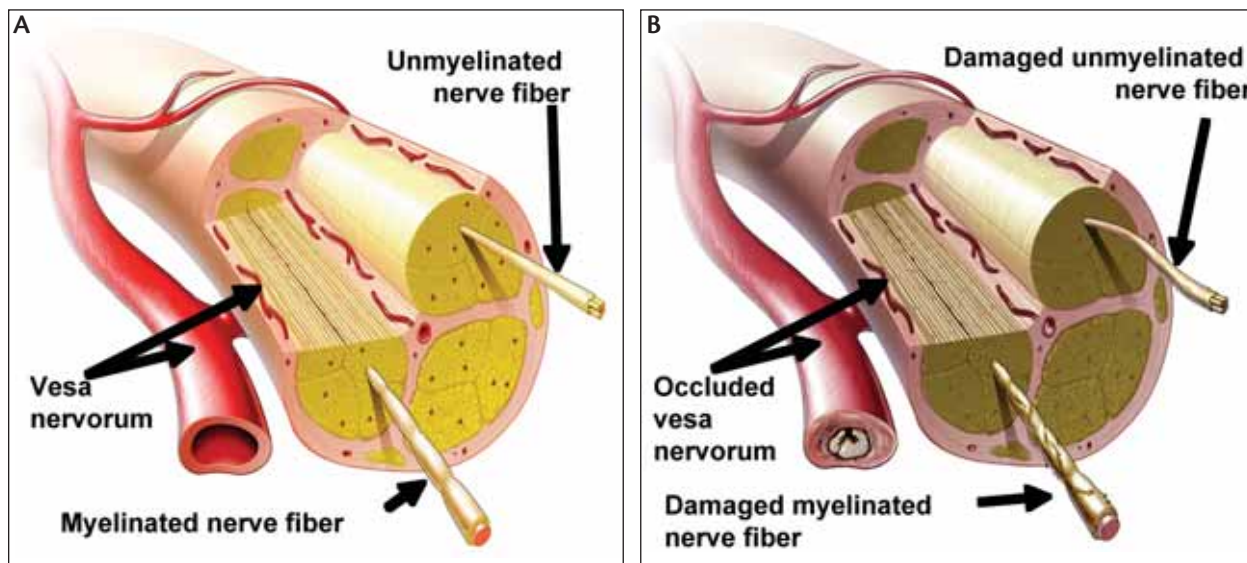


Figure 2. These illustrations show the difference between healthy nerves and blood vessels (A) and nerves and blood vessels damaged by DPN (B).

Among diabetic patients who show evidence of neuropathy on electrophysiological testing, only about half have physical findings and about 25% have symptoms. Therefore, neuropathy is commonly underdiagnosed. Herman and Kennedy² reported findings from 7,892 patients enrolled in the Glycemic Optimization with Algorithms and Labs at Point of Care (GOAL A1C) Study. Physicians reported an 18% prevalence of neuropathy in this group; subsequent monofilament testing detected no neuropathy in 63%, mild/moderate neuropathy in 30% and severe neuropathy in 7%. The physician perception and monofilament testing were concordant in 14% of patients. Nonendocrinologists correctly identified mild/moderate and severe neuropathy in 31% and 64% of patients, respectively. Endocrinologists correctly identified mild/moderate and severe neuropathy in 36% and 74% of patients, respectively.

There clearly is a need for training and education in



Figure 3. Wasting of the small muscles in the hands and feet puts one at risk for claw toe deformity.

the physical examination, which is now becoming a dinosaur in medicine.

CLASSIFICATIONS OF NEUROPATHY

The clinical classification of neuropathies includes either focal or diffuse. Diffuse neuropathies can be either proximal or distal, and distal neuropathies can be either large fiber or small fiber. Examples of focal neuropathies are mononeuritis and entrapment.

Mononeuritis is a sudden onset condition that usually involves a single nerve, but may be multiple. Common nerves of involvement are the C3, 6, 7, ulnar, median and peroneal. Mononeuritis is not progressive, and it resolves spontaneously, so treatment is symptomatic. Entrapment has gradual onset and involves single nerves exposed to trauma. Common nerves of involvement are the median, ulnar, peroneal, medial and lateral plantar. Entrapment is progressive, and treatment includes rest, splints, diuretics, steroid injections and surgery for failed medical therapy and weakness.

Characteristics of large-fiber, distal, symmetric diabetic neuropathies are weakness, wasting, impaired vibration detection, loss of position sense, loss of reflexes and interference with quality of life and activities of daily living. Small-fiber neuropathy is associated with pain, autonomic and thermal impairment, patients have normal strength and reflexes, it is electrophysiologically silent and produces symptoms leading to morbidity and mortality.

Large-fiber neuropathy. The clinical presentation of large-fiber neuropathy is impaired vibration detection, a

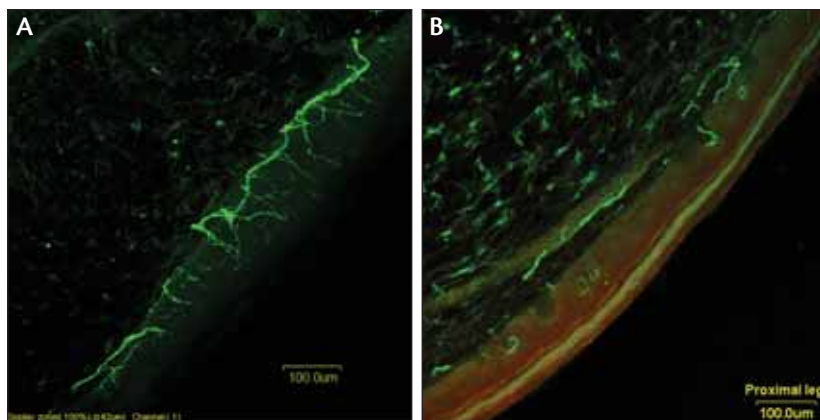


Figure 4. These images illustrate diabetes as a small-fiber disease. The photo on the left (A) is from a normal control patient and right (B) is a diabetic patients. (Images from Pittenger, et al. *Diabetes Care*. 2004;27:1974-1979.)

Small-fiber neuropathy. Small-fiber neuropathy presents as a C-fiber type pain, with superficial allodynia.⁷ Patients have early hyperesthesia, hyperalgesia, impaired neurovascular function, as well as late hypoesthesia and hypoalgesia. Clinical presentation also consists of impaired warm thermal and pain thresholds, decreased intraepidermal nerve fibers, decreased sweating, but normal strength, reflexes and electromyography (Figure 4).

Management options for small-fiber neuropathies include education, padded socks and appropriate shoes with adequate support.

deep-seated gnawing pain, numbness, ataxia, wasting of small muscles in the hands and feet, and increased blood flow. There is a risk of Charcot neuroarthropathy (Figure 3).

An additional concern with large-fiber neuropathy is its effect on falls. Patients with diabetic neuropathy are 15 times more likely to fall.³ Older patients often have a loss of vibration detection coupled with weakness of foot dorsiflexion.⁴ The cause of fractures in these cases is diabetic neuropathy, not osteopenia. The treatment is strength and balance training.

In older patients, strength training is associated with improved handgrip, leg press, knee extension, foot dorsiflexion and extension.^{5,6} Balance training improves backward tandem walking, and the combined training also improves neurovascular function.

Management options for large-fiber neuropathies includes proper shoes, orthotics, muscle strength and coordination building, bisphosphonates, tendon lengthening and surgical reconstructions.

Patients should have regular shoe and foot inspection — consider giving the patient a monofilament and a mirror to place on the floor in the bathroom. Emollients should be used to avoid dryness of sympathetic dysfunction.

IMPAIRED GLUCOSE TOLERANCE AND NEUROPATHY

Several studies have shown a link between impaired glucose tolerance (IGT) and neuropathy. In a prospective screening of patients with idiopathic sensory neuropathy, 30% to 50% have impaired glucose tolerance.⁸ IGT neuropathy is similar to early diabetic neuropathy, according to another study of 669 patients.⁹ In this group, 60% had sensory problems, 40% were impotent and 33% had autonomic involvement.

To manage IGT, it is recommended that patients reduce their body weight by 5% to 7% and increase aero-

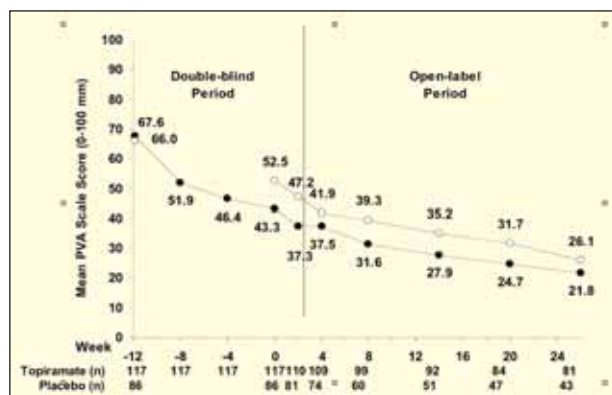


Figure 5. Durable effects of topiramate in neuropathic pain. (Data from Vinik, et al. *Neurology*. 2004;63:865-873.)

TABLE 1. RISK FACTORS FOR NEUROPATHY AFTER ADJUSTMENT FOR HBA1C AND DIABETES DURATION		
Variable	Odds Ratio	P value
CVD	2.74	<.0001
Albuminuria	1.48	.02
Hypertension	1.92	<.001
Smoking	1.55	<.001
BMI	1.40	<.001
Triglycerides	1.35	<.001
Total cholesterol	1.26	.001
LDL	1.22	.001

Source: Tesfaye et al. *N Engl J Med*. 2005;352:341-350.

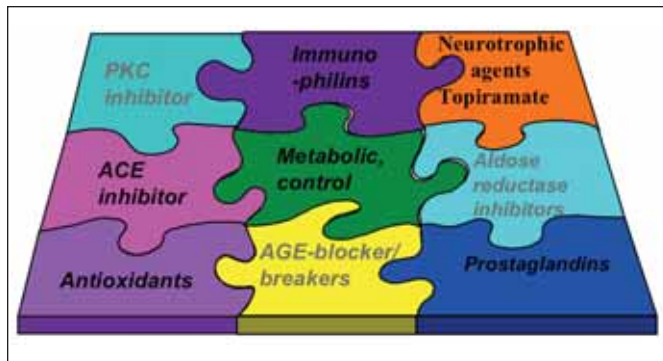


Figure 6. The armamentarium for treating diabetic neuropathic pain includes many different treatment options.

bic exercise to 150 minutes per week. These modest but attainable goals are considered prevention therapy.¹⁰⁻¹² Patients should work with both a nutritionist and an exercise physiologist, and pain should be treated as it would in diabetic peripheral neuropathy. Patients should have an oral glucose tolerance test (OGTT) repeated yearly; however, there are no data as to whether IGT neuropathy patients are more likely to convert to diabetes. The likelihood of conversion to diabetes increased with higher 2-hour OGTT values. Patients should be examined for macrovascular risk factors and metabolic syndrome and treated accordingly (Table 1).

SIMPLE INTERVENTIONS

Simple interventions can reduce serious lesions in type 2 diabetic patients. Studies have shown a 60% reduction in lesions when patients are educated regarding proper foot care. Patients enter the clinic without shoes on, in order to ensure that their feet are examined as well as their shoes. They are then provided with written information about foot care, a monofilament and a mirror for the bathroom floor.^{13,14}

Can Nerve Fibers Degenerate and Regenerate? Topiramate (Topamax; Ortho-McNeil Neurologics, Titusville, NJ) is a new neuroprotective agent that shows promise in the treatment of painful diabetic neuropathy (Figure 5).^{15,16} It is a sulfamate-substituted monosaccharide that may inhibit phosphorylation. It also

- blocks voltage-activated sodium⁺ channels,
- increases GABA-evoked currents,
- decreases kainate-evoked channels,
- inhibits high-voltage activated calcium⁺⁺ channels and
- inhibits carbonic anhydrase.

Topiramate is approved for the treatment of seizure — partial or generalized tonic-clonic and migraine. Observational studies in humans indicate weight loss

as well. Topiramate may also stimulate nerve regeneration.

Two other recent additions to our armamentarium (Figure 6) for the treatment of neuropathic pain include duloxetine (Cymbalta; Eli Lilly and Company, Indianapolis, Ind) and pregabalin (Lyrica; Pfizer, New York, NY). Duloxetine was Food and Drug Administration (FDA) approved in September 2004. It is a balanced, potent serotonin and norepinephrine reuptake inhibitor, and it was the first such treatment approved for the management of diabetic peripheral neuropathic pain. In clinical studies, according to Lilly, duloxetine significantly reduced 24-hour average pain, with improvements noted as early as the first week of treatment. The agent showed rapid onset of action and sustained effect and was effective for relieving nighttime pain.

Pregabalin was approved by the FDA on Dec. 31, 2004. It provides rapid and sustained relief via a newly defined mechanism of action, according to Pfizer. Its efficacy was established in clinical trials of more than 9,000 patients. ■

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