

Recent advances in the treatment of diabetic neuropathy

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Purpose of review

Diabetic neuropathies are a complex, heterogeneous group of disorders that include a wide range of abnormalities. They can be focal or diffuse, proximal or distal, affecting both somatic and autonomic nervous systems. Diabetic neuropathy causes considerable morbidity and mortality and reduces the quality of life and activities of daily living of the individual with diabetes. Management of the disease is complex and requires targeted intervention. This review summarizes the recent advances in the treatment of both symptoms and the underlying pathophysiology of diabetic neuropathy.

Recent findings

There has been an increasing understanding of the pathogenesis of diabetic neuropathy in recent years, and new drugs that target the pathophysiological mechanisms are currently being studied. Pain mechanisms for the different types of pain syndromes are also more completely understood, and two drugs have recently been approved in the United States for the treatment of the neuropathic pain of diabetes.

Summary

As knowledge of the underlying pathophysiological mechanisms continues to grow, symptomatic therapy is now available, and newer and better treatment modalities based on causal factors are being explored with the potential for a significant impact on morbidity and mortality.

Keywords

diabetic neuropathy, pain, treatment

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Abbreviations

| | |
|-------------|---|
| AGE | advanced glycation end-product |
| ARI | aldose reductase inhibitor |
| DPN | diabetic peripheral neuropathy |
| MGUS | monoclonal gammopathy of unknown significance |
| NCV | nerve conduction velocity |
| NGF | nerve growth factor |
| PKC | protein kinase C |
| SNRI | serotonin and norepinephrine reuptake inhibitor |
| VEGF | vascular endothelial growth factor |

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Introduction

Diabetic neuropathies are a heterogeneous group of conditions that involve different parts of the somatic and autonomic nervous systems. They can be focal or diffuse, proximal or distal. The pathogenesis is also heterogeneous, with different causative factors, including persistent hyperglycemia, microvascular insufficiency, oxidative stress, nitrosative stress, defective neurotrophism, and autoimmune-mediated nerve destruction [1^{••}–3^{••}].

This review will focus on recent advances in the treatment of diabetic neuropathy.

Diagnosis: definition and classification

Diabetic neuropathy is the presence of symptoms or signs of peripheral nerve dysfunction in individuals with diabetes after the exclusion of other causes. Confirmation may require abnormalities in nerve conduction studies, quantitative sensory or autonomic tests or even histology of intraepidermal nerves in skin biopsies [3^{••}]. A working clinical classification is provided in Table 1 [1^{••}].

Endocrinologists and non-endocrinologists are approximately equivalent in their ability to identify neuropathy. They recognize the absence of neuropathy 90% of the time, but fail to detect severe neuropathy 25% and mild neuropathy 65% of the time [4]. A recent American Diabetes Association omnibus survey of 8119 individuals [3^{••}] showed that only one out of four individuals with neuropathy had discussed this with their physician – an appalling indictment of failure of the healthcare system or the physician–patient relationship. The simplest bedside test is a 128 Hz tuning fork or a patella hammer, but these were used less than 10% of the time by physicians. Clearly, there is a huge hiatus in physician education for the management of neuropathy. Much of this relates to their feeling of inadequacy and the lack of available therapies until now.

Treatment

Figure 1 [5] illustrates the complex mechanisms leading to nerve dysfunction. These include metabolic abnormalities, microvascular insufficiency, autoimmune mechanisms and deficiencies of neurotrophism.

Treatment of specific underlying pathogenic mechanisms: glycemic and metabolic control

Numerous studies have shown a tight relationship between hyperglycemia and the development and

Table 1 Classification of diabetic neuropathies

| | |
|--|--|
| Rapidly reversible Generalized symmetrical PN | Hyperglycemic neuropathy Acute sensory Chronic sensorimotor (DPN) Small-fiber neuropathy Large-fiber neuropathy Autonomic |
| Focal and multifocal neuropathies | Cranial Thoracolumbar radiculoneuropathy Focal limb Proximal motor (amyotrophy) Co-existing CIDP |

CIDP, chronic inflammatory demyelinating neuropathy; DPN, diabetic peripheral neuropathy; PN, peripheral neuropathy.

severity of diabetic neuropathy. Both the Diabetes Control and Complications Trial (DCCT) [6] and the UK Prospective Diabetes Study (UKPDS) [7] showed that intensive glycemic control was associated with a 40–60% reduction in the development or progression of neuropathy. For every 1% reduction there was a 22–37% decrease in microvascular complications. Of greater relevance was the Epidemiology of Diabetes Interventions and Complications study (EDIC) [8] and post-UKPDS study, which demonstrated that the reduction in complications persisted despite a return of hemoglobin A1c to pretreatment levels – a curve now known as the Nike curve of diabetes treatment. A similar observation has been presented for the UKPDS study by LeRoith

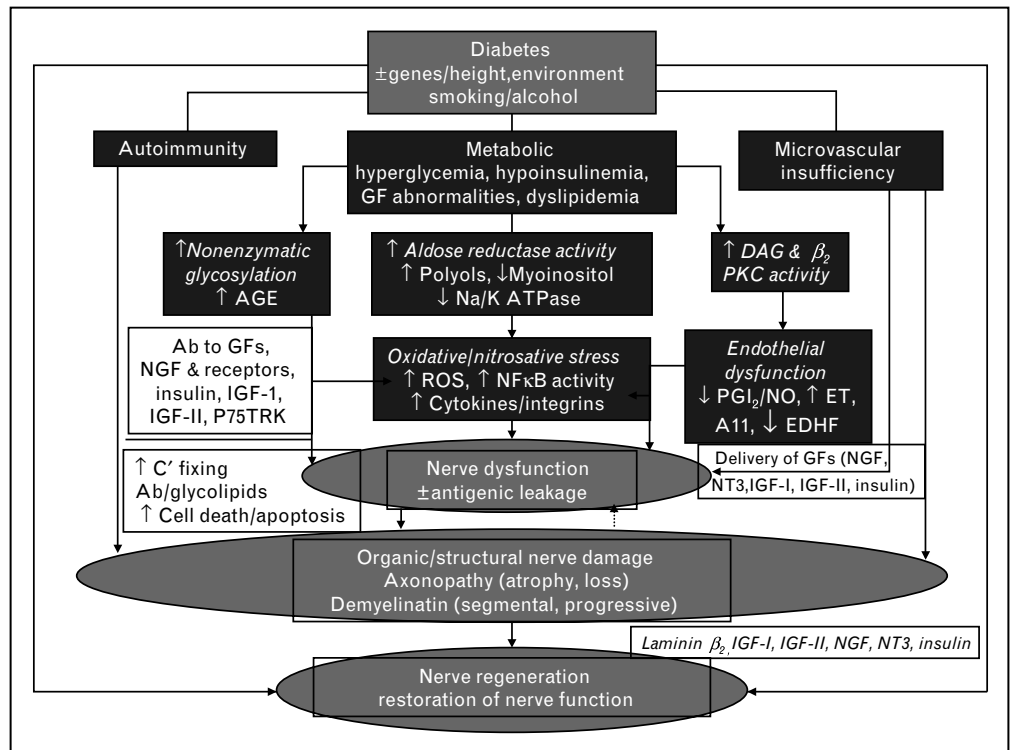
et al. [9]. This makes a strong case for aggressive early intervention to see later rewards. The natural history of diabetic neuropathy is changing. Several randomized trials have shown no deterioration of neuropathy after 1–4 years [10,11]. To what can these effects of placebo be attributed? Tesfaye *et al.* [12*], in the EURODIAB prospective study that included 3250 patients across Europe, has shown that the incidence of neuropathy is also associated with potentially modifiable cardiovascular risk factors, including raised triglyceride levels and body mass index, smoking, and hypertension. Several of the risk factors that were found in that study were components of the metabolic syndrome. The Steno trial [13], using multifactorial intervention, reported a reduction in the odds ratio to 0.32 for the development of autonomic neuropathy. Therefore, treatment of neuropathy should include measures to reduce macrovascular risk factors, including hyperglycemia, blood pressure and lipid control, and lifestyle modifications including exercise and weight reduction, smoking cessation, a diet rich in omega-3 fatty acids and the avoidance of excess alcohol consumption. Perhaps some of these factors have changed the natural history of diabetic neuropathy, but this needs to be explored further.

Oxidative and nitrosative stress

A number of studies have shown that hyperglycemia causes oxidative and nitrosative stress in tissues that

Figure 1 Pathogenesis of diabetic neuropathies

Ab, Antibody; AGE, advanced glycation end-product; ATPase, adenosine triphosphatase; DAG, diacylglycerol; EDHF, endothelial-derived hyperpolarizing factor; ET, endothelin; GF, growth factor; IGF, insulin-like growth factor; K, potassium; Na, sodium; NFκB, nuclear factor kappa B; NGF, nerve growth factor; NO, nitric oxide; NT3, neurotrophin 3; PGI₂, prostaglandin I; PKC, protein kinase C; ROS, reactive oxygen species. Reproduced from Vinik *et al.* [5], with permission.



are susceptible to the complications of diabetes, including peripheral nerves. Oxidative stress leads to the generation of free radicals that can affect lipids present in the myelinated structures of nerves. It has been shown that hyperglycemia induces an increase in superoxide and peroxynitrite ions, and that antioxidant defense moieties are reduced in diabetic neuropathy [14]. The increased production of nitrates combine with reactive oxygen species to form peroxynitrate, which can be highly damaging to nerves [14–16]. The end-result of this oxidative/nitrosative assault is the loss of axons and disruption of the microvasculature in the peripheral nervous system (Fig. 1). Therefore, it is reasonable to use therapies that are known to reduce oxidative and nitrosative stress [16]. Agents that have been tried with some success include aldose reductase inhibitors (ARIs), alpha lipoic acid, gamma linolenic acid, benfotiamine and protein kinase C inhibitors.

Alpha-lipoic acid or thioctic acid has been used for its antioxidant properties and for its thiol-replenishing, redox-modulating properties. It has been shown to prevent or ameliorate experimental diabetic neuropathy [17]. A number of randomized, placebo-controlled studies have been published. A recent meta-analysis [11], including 1258 patients, showed that it has a favorable influence on reducing neuropathic symptoms. An improvement in cardiac autonomic neuropathy was also demonstrated. Preliminary data over 2 years also indicated a possible long-term improvement in motor and sensory nerve conduction velocities (NCVs) in the lower limbs. A large multicenter trial has been completed in north America and Europe evaluating the effects of long-term treatment with alpha-lipoic acid over 4 years on the progression of diabetic neuropathy. Although it failed to achieve the designated endpoints, salutary effects were observed so that this approach should not be dismissed prematurely.

Advanced glycation end-products (AGEs) have been implicated in the development of neuropathy by binding to a specific receptor (RAGE) initiating a cascade of events culminating in nerve damage [18]. Aminoguanidine – an inhibitor of AGE formation – showed good results in animal studies, but trials in humans have been discontinued because of toxicity. Gamma-linolenic acid can cause a significant improvement in clinical and electrophysiological tests for neuropathy. Benfotiamine, a vitamin B1 analog, may decrease the accumulation of sugar phosphates, leading to a decrease in AGE formation. Cameron *et al.* [19] treated streptozotocin-induced diabetic rats with benfotiamine and showed an improvement in endoneurial blood flow and NCV.

ARIs reduce the flux of glucose through the polyol pathway, inhibiting tissue accumulation of sorbitol and

fructose. Numerous agents have been evaluated over the past 20 years but most have not been licensed because of serious adverse events (tolrestat, zenarestat) or a lack of efficacy (ponalrestat, zenarestat). In a 1-year trial of fidarestat in Japanese diabetic patients [20], an improvement of symptoms was shown and a 3-year study of epalrestat showed improved nerve function (NCV) as well as vibration perception. Bril and Buchanan [21] reported on the administration of a new ARI, AS-3201. After 12 weeks there was a decrease in nerve sorbitol in a dose-dependent fashion, with a trend towards an improvement of NCV and clinical signs and symptoms. The open label extension of the study supported a role for this ARI in the treatment of diabetic neuropathy. This has stimulated a resurgence of interest, and new ARIs are currently being explored, but it is becoming clear that these agents may be insufficient *per se* and combinations of treatments may be needed [1**].

Protein kinase C beta inhibition

Neural vascular insufficiency has been proposed as a contributing factor to the development of diabetic neuropathy. Protein kinase C (PKC) activation is a critical step in the pathway to diabetic microvascular complications [22]. Preclinical studies in animal diabetes models using ruboxistaurin mesylate (LY333531) – a PKC β inhibitor – have shown an improvement in many diabetes-related changes in vascular function such as retinal blood flow [23], endoneurial blood flow and NCV [24,25]. A multinational, randomized, phase 2, double-blind, placebo-controlled trial was conducted for 1 year to test the efficacy and tolerability of ruboxistaurin in patients with diabetic neuropathy. Preliminary results failed to achieve the endpoints, but showed a statistically significant improvement in symptoms in ruboxistaurin-treated neuropathy groups with a sural nerve action potential greater than 0.5 μ V at baseline compared with placebo [10]. The change from baseline for the vibratory detection threshold was statistically significantly improved in the treated groups [26]. The drug was well tolerated and there were no differences in the number of reported adverse events. The phase 3 study failed to achieve its primary endpoint – symptom reduction – after 1 year; however, studies are ongoing that will determine the effects of the PKC inhibitors on objective measures of neurological function over a longer period of time.

Growth factors

Increasing evidence exists that there is a deficiency of growth factors such as nerve growth factor (NGF) in diabetes, as well as the dependent neuropeptides substance P and calcitonin gene-related peptide, and that this contributes to the clinical perturbations in small fiber function [27]. Clinical trials with NGF and neurotrophin 3 have not been successful but are subject to certain caveats with regard to design. For example, the neurotrophin 3 trial

was a phase 2 study on tolerability and was not powered for efficacy, but was interpreted as negative. The NGF phase 2 study was successful using a few highly specialized sites and small fiber endpoints. The phase 3 study used many more inexperienced sites, combined small and large fiber endpoints, and had problems with blinding and patient selection. NGF and neurotrophin 3 thus still hold promise for sensory and autonomic neuropathies. The most potent stimulus for angiogenesis is vascular endothelial growth factor (VEGF). A reduction in VEGF activity in streptozotocin-diabetic mice results in the failure of neovascularization in hypoxic tissue in the lower limb [28,29]. An intramuscular injection of an adenoviral vector encoding for VEGF induces normal neovascularization in the hindlimb. C-peptide, considered to be a waste product of insulin biosynthesis, has neuroprotective properties. These compounds are in clinical development for diabetic neuropathy.

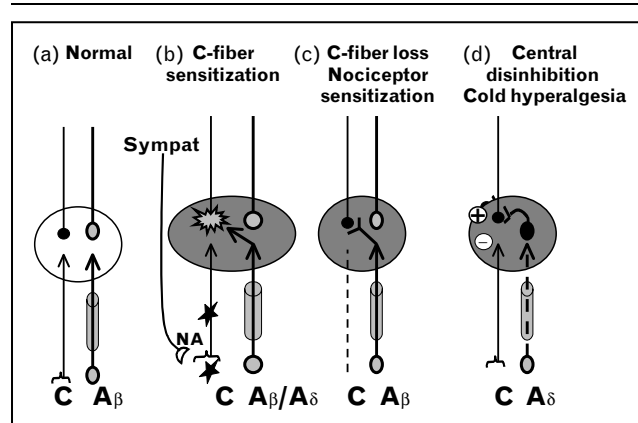
Immune therapy

An 11-fold increased likelihood exists of chronic inflammatory demyelinating polyneuropathy, multiple motor polyneuropathy, vasculitis and monoclonal gammopathy of unknown significance (MGUS) in diabetes [30], which respond to immune therapy [31,32]. New data support a predictive role for the presence of antineuronal antibodies on the later development of neuropathy, and these may not be innocent bystanders but neurotoxins [33,34^{*}]. Patients with predominantly motor features may have chronic inflammatory demyelinating polyneuropathy or MGUS or antibodies to monosialoglycosides [35]. If serum immunoelectrophoresis indicates that MGUS or circulating antibodies to neurons (motor sensory profile) are present, immune therapy is indicated. Selected cases with autonomic neuropathy may benefit from intravenous immunoglobulin treatment, such as the recent case of a patient with orthostatic hypotension secondary to antibodies to the acetylcholine receptor. He showed a remarkable improvement with exchange transfusion and removal of the circulating antibodies [36]. If the duration of diabetes is short and the autonomic neuropathy severe, suspect an autoimmune cause.

Treatment of symptoms and improvement in quality of life

The control of pain symptoms constitutes one of the most difficult management issues in diabetic neuropathy. A careful history of the nature of pain, its exact location and a detailed examination of the lower limbs is mandatory to ascertain alternative causes of pain. The conditions that mimic diabetic neuropathy include neuromas, fasciitis, entrapments, claudication and arthritis, and must be excluded. Neuropathic pain is distinct from nociceptive and inflammatory pain, which are protective. Neuropathic pain is not protective, arises spontaneously, and is caused by the dysfunction of different nerve fiber types

Figure 2 Schematic representation of the generation of pain

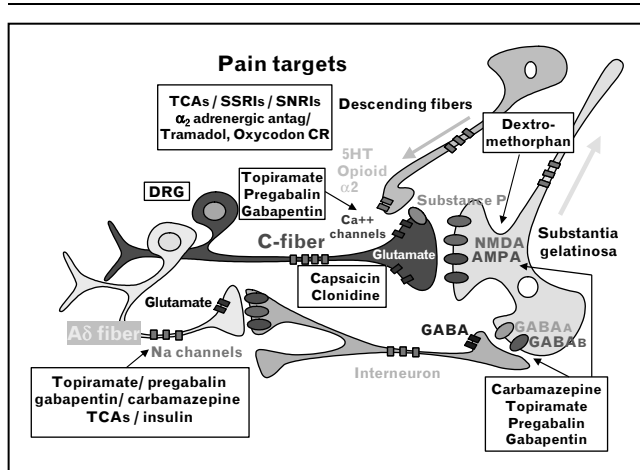


(a) Central terminals of c-afferents project into the dorsal horn and make contact with secondary pain-signaling neurons. Mechanoreceptive A β afferents project without synaptic transmission into the dorsal columns (not shown), and also contact secondary afferent dorsal horn neurons. (b) Spontaneous activity in peripheral nociceptors (peripheral sensitization, black stars) induces changes in the central sensory processing, leading to spinal cord hyperexcitability (central sensitization, white star) that causes input from mechanoreceptive A β (light touch) and A δ fibers (punctuate stimuli) to be perceived as pain (allodynia). (c) C-nociceptor degeneration and novel synaptic contacts of A β fibers with 'free' central nociceptive neurons, causing dynamic mechanical allodynia. (d) Selective damage of cold-sensitive A δ fibers that leads to central disinhibition, resulting in cold hyperalgesia [1^{**}].

(A-delta and C fibers), which are modulated by sympathetic input, with spontaneous firing and the release of different neurotransmitters at neuronal synapses and connections to the dorsal root ganglia, spinal cord and cerebral cortex. Figure 2 describes the pathophysiological basis for the generation of neuropathic pain. Different types of pain respond to different types of therapies [1^{**}]. Figure 3 describes the different nerve fibers affected and possible targeted treatments.

Antidepressants in neuropathy

Recent interest has focused on antidepressants with dual selective inhibition of serotonin and norepinephrine (serotonin and norepinephrine reuptake inhibitors; SNRIs), such as duloxetine and venlafaxine. Duloxetine has recently been approved for neuropathic pain in the United States. It is a selective, balanced and potent SNRI in the brain and spinal cord, thus leading to increased neuronal activity in efferent inhibitory pathways. In clinical trials, 58% of individuals reported at least a 30% sustained reduction of pain [37]. Raskin *et al.* [38] evaluated the effect of duloxetine in 348 patients with diabetic neuropathy for 12 weeks. Doses of 60 and 120 mg were effective and well tolerated in the treatment of diabetic neuropathy [38]. The most commonly reported side-effects in clinical trials were nausea, dry mouth, constipation, and diarrhea. It is important to know that physicians must be alert to suicidal ideation and an

Figure 3 Different mechanisms of pain and possible treatments

C fibers are modulated by sympathetic input with the spontaneous firing of different neurotransmitters to the dorsal root ganglia (DRG), spinal cord and cerebral cortex. Sympathetic blockers (clonidine) and depletion of axonal substance P (SP) used by C-fibers as their neurotransmitter (capsaicin) may improve pain. In contrast A δ fibers utilize sodium (Na) channels for their conduction and agents that inhibit sodium exchange such as antiepileptic drugs, tricyclic antidepressants (TCAs) and insulin may ameliorate this form of pain. Anticonvulsants (carbamazepine and topiramate) potentiate γ -aminobutyric acid (GABA) activity, inhibit sodium and calcium (Ca) channels and inhibit *N*-methyl-D-aspartate (NMDA) and α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors. Pregabalin appears to modulate the $\alpha 2 \delta 1$ subunit of the calcium channel on presynaptic neurons, decreasing the release of excitatory neurotransmitters. Dextromethorphan blocks NMDA receptors in the spinal cord. TCAs, selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) inhibit serotonin and norepinephrine reuptake, enhancing their effect in endogenous pain-inhibitory systems in the brain. Tramadol is a central opioid analgesic [1*]. 5HT, 5-Hydroxytryptamine (serotonin).

exacerbation of autonomic symptoms as well as aggravation of depression.

Anticonvulsants in diabetic neuropathy

Anticonvulsants have stood the test of time in the treatment of diabetic neuropathy [39]. The principal mechanisms of action include sodium channel blockade, the potentiation of γ -amino butyric acid activity, calcium channel blockade, antagonism of glutamate at *N*-methyl-D-aspartate receptors or α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid [40].

Pregabalin is a γ -amino butyric acid analog with similar structure and actions to gabapentin. It has anti-epileptic, analgesic and anxiolytic activity. The exact mechanism of action is unclear, although it may reduce excitatory neurotransmitter release by binding to the $\alpha 2$ - δ protein subunit of voltage-gated calcium channels. In a randomized, placebo-controlled, multicenter study including 140 patients, pregabalin produced significant improvements on pain scores within one week of treatment ($P < 0.01$), which persisted for 8 weeks ($P < 0.01$). Furthermore, 40% of patients receiving pregabalin reported a 50% or

greater reduction in pain, compared with 14.5% of the placebo group ($P = 0.001$) [41]. Another study [42], conducted by the same group, in 338 patients, showed an improvement in endpoint mean pain scores with doses of 300 and 600 mg/day compared with placebo ($P = 0.0001$) at 5 weeks. Pregabalin also showed a beneficial effect on sleep [42]. A 12-week flexible compared with fixed-dosage study [43] of 249 patients with diabetic neuropathy showed a responder rate (defined as $\geq 50\%$ pain relief) of 48.2% in the flexible-dosage group, 52.3% in the fixed-dosage group and 24.4% in the placebo group [43]. The drug was well tolerated in all three studies, and the most common adverse events were dizziness, somnolence and peripheral edema.

In a 12-week randomized, placebo-controlled multicenter study [44] ($n = 214$) with topiramate, there was a 50% improvement in symptoms in the topiramate group compared with 34% in the placebo group ($P < 0.004$). Topiramate also reduced pain intensity compared with placebo ($P < 0.003$) as well as sleep disruption scores ($P < 0.02$). In a small within-subject study conducted by us [45], this drug also reduced body weight, improved nerve conduction amplitudes, increased intraepidermal nerve fibers, lowered blood pressure and had a favorable impact on lipids and insulin resistance. It thus seems that topiramate may be one of the few drugs to show potential for altering the basic biological nerve dysfunction in diabetic neuropathy [46*].

Pain symptoms in neuropathy significantly impact quality of life [45], and it appears that pain is associated with anxiety and depression or apathy, with weakness, ataxia and instability. The symptomatic therapy of neuropathy can be challenging, and the selection of pain medication and dosages must be individualized, with attention to their potential side-effects and drug–drug interactions. Ultimately, treatment should be holistic and address the underlying disorder, as well as directing efforts to the factors that compromise lifestyle. As the great diabetologist R.D. Lawrence said: ‘Painful diabetic neuropathy interferes with work.’

Adjunctive management and treatment of complications

Large fiber neuropathy is manifested by reduced vibration perception and position sense, weakness, muscle wasting and depressed deep tendon reflexes. Diabetic patients with large fiber neuropathies are uncoordinated and ataxic, and are 17 times more likely to fall than their non-neuropathic counterparts. It is therefore important to improve strength and balance in patients with large fiber neuropathy. Patients can benefit from high-intensity strength training by increasing muscle strength, improving coordination and balance, and thus reducing falls and the risk of fractures [47]. Low-impact activities, which emphasize muscular strength and

coordination, and challenge the vestibular system, such as Pilates, yoga, and Tai Chi may also be particularly helpful. In addition, proper orthotics are needed to prevent foot deformities. Surgery may be required for tendon lengthening in equinus deformities. Reconstruction and full contact casting can also be tried.

Conclusion

Somatic and autonomic neuropathies (diabetic peripheral neuropathy; DPN) are among the most common long-term complications of diabetes and its precursors, impaired glucose tolerance and the metabolic syndrome. DPN is associated with considerable morbidity and mortality and with a significant impact on quality of life. It is highly prevalent in diabetic populations, although is often not recognized by physicians. The management of the disease is complex, and the key to success depends partly on discovering the underlying pathological processes in each particular clinical presentation. There has been increasing understanding of the pathogenesis of DPN, and new drugs that target the pathophysiological mechanisms are currently being studied. Pain mechanisms for the different types of pain syndromes are also more completely understood, and two drugs have recently been approved in the United States for the treatment of the neuropathic pain of diabetes. Two decades ago physicians could only diagnose DPN and commiserate with the patient. This has changed in the past few years with increasingly available therapies as the knowledge of the condition continues to grow.

Author's opinion

A whole lot more can be done for diabetic neuropathy other than make the diagnosis and commiserate with the patient. Proximal, predominately motor neuropathies are inflammatory and respond to immunotherapy. Focal neuropathies may be mononeuritis that require no intervention, heal spontaneously, and 30% of individuals with diabetes have entrapment syndromes, e.g. carpal tunnel, which can be relieved with splints, diuretics and injections of local anesthetics or steroids. Pain in diabetic neuropathy is small or large-fiber in type or mixed. For small-fiber pain simple analgesics are the first choice followed by topical treatment. For large-fiber pain, the tricyclic antidepressants and antiepileptic drugs, e.g. topiramate, lamotrigine and pregabalin, are favored. For lightning pain, carbamazepine is preferred. When these fail, dextromethorphan or an SNRI, e.g. duloxetine, can be added. If the pain has mixed qualities, combinations of drugs from different classes may be used. Whereas there is great hope in the use of magnets, stochastic resonance, electrical stimulation, high frequency muscle stimulation and infrared therapy, all of which purport to have 100% success, the problem resides in distinguishing their effects from placebo. Patients with pain have a 30% reduction 30% of the time in clinical

trials. 'Entering patients into a clinical trial may be a good algorithm for the initial approach to neuropathic pain.'

Ultimately one needs to address the underlying disease. Topiramate causes nerve regeneration. Promising trials with aldose-reductase inhibitors, antioxidants and neurotrophic agents exist. Until we can abrogate the progression and reverse the underlying disorder, our job is not done.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 215–216).

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