# *Managing Diabetic Polyneuropathy*

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Of the various end-organs affected by prolonged dysglycemia, whether in the form of impaired glucose tolerance (IGT) or frank diabetes (Types 1 or 2), the peripheral nervous system (PNS) is particularly vulnerable.[1] Thus, diabetic polyneuropathy (DPN) is a leading cause of morbidity and non-traumatic amputations within this population. While risk factors for the development of DPN are established (Table 1), additional cryptogenic factors must influence the expression of neuropathic symptoms. For example, while up to 50% of all causes of peripheral neuropathy are related to diabetes, in nearly one third of patients the exact etiology remains uncertain. Amongst these patients 40% will manifest IGT.[2] By contrast, Pirart *et al.*[3] documented that 50% of patients who had diabetes for 25 years had no evidence of DPN. Therefore, two distinct groups emerge, one ultra-sensitive to elevated blood sugar and the other relatively protected against it. Despite such wide variability in terms of time-to-onset once symptoms develop the pattern is characteristic.

**Table 1**

**Modifiable and non-modifiable risk factors for the development of Diabetic Polyneuropathy**

| Modifiable | Non-modifiable |
|---|---|
| Poor glycemic control | Older age |
| Alcohol | Male |
| Hypertension | Height |
| Hyperlipidemia | Disease duration |
| Smoking | Apolipoprotein E 4 genotype |
| | (Type 1 myotonic dystrophy [DM1] only) |
| | Aldose reductase hyperactivity |
| | ACE genotype |

## *What are some clinical features?*

DPN is a slowly progressive, length-dependent neuropathy affecting primarily sensory fibers of both large (*i.e.*, slowed nerve conduction, distal hypesthesia and reduced balance) and small (*i.e.*, pain, autonomic dysfunction and reduced intra-epidermal nerve fiber density) caliber. Motor fibers are affected later in the course. Positive symptoms consist of tingling, thermal (burning and/or freezing) and electric dysesthesias. Negative symptoms consist of numbness, weakness and impaired proprioception. Recent evidence suggests that even in the "pre-diabetic" state deficits in standing balance and trunk position sense are discernable.[4]

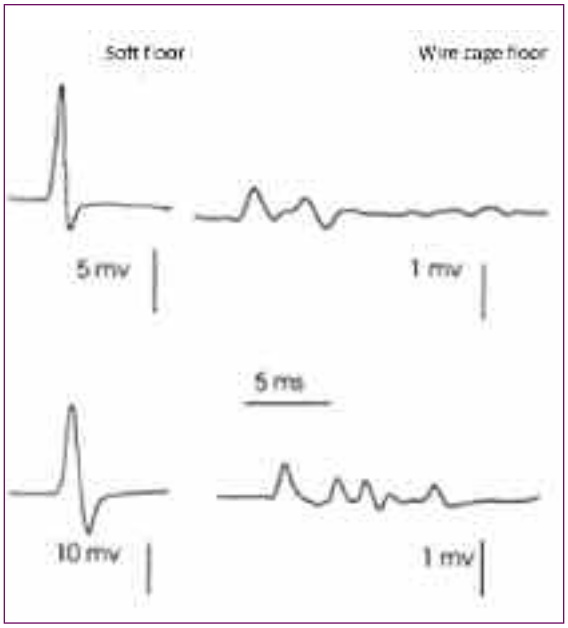

Figure 1. Tracings are CMAPs from tibial-innervated muscles in rats reared in cages with wire flooring.

## What are variant forms of diabetic neuropathy?

While DPN is the most common form of diabetic neuropathy other forms are described. Small fiber neuropathy can develop in the context of IGT and evades detection by conventional nerve conduction studies as these assess only the large fibers. As motor fibers are exclusively large, diameter small fiber degeneration is a sensory autonomic disorder. Autonomic dysfunction is usually present and can be severe. After 10 to 15 years of disease 30% of diabetics will manifest abnormal cardiac beat-to-beat variability.[5] Reduced gut motility, resulting in constipation and diarrhea—due to bacterial overgrowth—are common GI manifestations. Small fiber neuropathy generally progresses to DPN but diet and exercise have been shown to improve symptoms. Focal and multifocal neuropathies are largely attributed to compression/entrapment at typical sites (*i.e.*, carpal tunnel, cubital tunnel, fibular head). Diabetic nerves are particularly susceptible to compression and ischemia as illustrated in Figure 1. However, rarer forms such as microvasculitis lumbosacral radiculoplexus neuropathy (also known as diabetic amyotrophy) targeting the upper or lower plexus can occur. Early treatment with steroid and IV immune globulin may be beneficial. The natural history is generally favorable but permanent severe weakness can occur. Thoracic radiculitis is a form of mononeuropathy that is likely a restricted variant of the plexopathy. Truncal pseudohernias can develop due to abdominal wall weakness. The absence of a previous surgery in a diabetic patient should point to this diagnosis. An ultrasound will not identify a ventral defect and an electromyography (EMG) will reveal evidence of denervation after approximately seven days. Several cranial neuropathies are known to occur in diabetics with pupil-sparing third nerve palsy being the most common. Cranial nerves IV, VI, VII and II are also susceptible. Lastly, whether chronic inflammatory demyelinating polyneuropathy (CIDP), a proximal upper-extremity motor predominant disease, differentially affects diabetics is uncertain. In severe diabetics nerve conduction velocities may be in the demyelinating range (arm: < 35 m/s; leg: < 30 m/s) however, when well-controlled Type 2 diabetics develop a demyelinating neuropathy, confirmed on electrodiagnostic testing, there is high likelihood of CIDP. Neuromuscular referral, lumbar puncture to assess for cerebrospinal fluid protein elevation and institution of immune therapy is warranted.

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## What are the treatments?

Painful DPN represents a major morbidity particularly when it evolves in the pre-diabetic state. Effectively managing this pain is possible for many yet a subset of individuals with painful DPN appear to be refractory to most drug therapies. Amongst the more commonly prescribed agents the tricyclic antidepressants (TCAs) (*i.e.*, amitriptyline, nortriptyline, desipramine and imipramine) are well proven. Serotonin noradrenaline reuptake inhibitors (SNRIs) such as venlafaxine and duloxetine have shown favourable results and are better tolerated than the TCAs. The selective serotonin reuptake inhibitors may offer modest benefit but conflicting reports detract from their first-line use. The antiepileptic drugs such as carbamazepine, phenytoin and valproic acid have demonstrated efficacy in ameliorating DPN-related pain, however in primary care these agents warrant greater vigilance regarding side-effect management and drug-drug interactions. The two ligands—gabapentin and pregabalin—have level 1 evidence supporting their ability to reduce pain and improve quality of life. Lack of drug coverage represents a major pragmatic obstacle limiting their more effective use in clinical practice. Finally, lipoic acid, a potent anti-oxidant, has been shown in several trials to improve painful DPN.[6,7] Preliminary evidence suggests that combination neutraceutical supplementation will offer further benefit but more work is required to clarify this.[8]

*DPN is a leading cause of morbidity and non-traumatic amputations within this population.*

## Conclusion

The management of DPN in the absence of pain necessarily focuses on controlling dysglycemia and attempting to restrain hemoglobin A1C < 7%. When neuropathic pain develops clinicians must attend to this troubling and at times devastating complaint. Indeed, effective communication is an integral part of long-term doctor-patient interactions. Patients must know that their healthcare provider understands their symptoms and is willing to approach their symptoms in a graded and knowledgeable fashion. Polypharmacy may be required with a combination of, for example, nortriptyline 50 mg h.s., gabapentin 300 mg t.i.d.-q.i.d. and lipoic acid 300 mg b.i.d.

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