

BRIEF CLINICAL UPDATE

Updates in Management of Diabetic Peripheral Neuropathy

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Diabetes mellitus is associated with several different patterns of nerve injury including distal sensorimotor polyneuropathy, lumbosacral radiculoplexus neuropathy, mononeuropathy or mononeuritis multiplex, and autonomic neuropathy. The common term diabetic peripheral neuropathy generally refers to a chronic, symmetrical, length-dependent sensorimotor polyneuropathy. In 2009 the Toronto Diabetic Neuropathy Expert Group¹ defined this condition as, “a symmetrical, length-dependent sensorimotor polyneuropathy attributable to metabolic and microvessel alterations as a result of chronic hyperglycemia exposure (diabetes) and cardiovascular risk covariates.” In 2017 the American Diabetes Association² provided the following definition, “the presence of symptoms and or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes.” Both large and small fiber dysfunction can occur. Diabetic peripheral neuropathy is classically characterized by a progressive loss of distal sensation, followed in some cases, by motor weakness. Symptoms tend to be nerve length dependent resulting in a stocking-glove distribution. Symptoms include tingling, burning, stabbing pain, and other abnormal sensations. Negative symptoms include sensory loss, weakness, and numbness. Symptoms may worsen with rest and at night. This syndrome often develops insidiously, and patients may be asymptomatic on initial presentation.

There is considerable variability in reported epidemiology of diabetic peripheral neuropathy due to patient selection bias, different diagnostic criteria, and use of different assessment methods across studies. The global prevalence of clinically diagnosed neuropathy in patients with diabetes mellitus is thought to exceed 30% while the lifetime incidence may be over 50%. Up to 50% of patients diagnosed with diabetic peripheral neuropathy may be asymptomatic. Up to one out of every four patients with diabetes mellitus develop painful symptoms. Neuropathy is not necessarily a late complication of diabetes mellitus as 11 to 13% of patients with prediabetes also have some peripheral neuropathy. Risk factors for the development of diabetic peripheral neuropathy include duration of diabetes mellitus, glycemic control, presence of insulin resistance, hypertension, adiposity, dyslipidemia, tobacco use, alcohol abuse, increased height, older age, and certain genetic polymorphisms.³

Our current understanding of the pathophysiologic mechanisms involved in the development of diabetic peripheral neuropathy remains incomplete though it is likely that multiple pathogenic mechanisms are involved.⁴ Both the peripheral neuronal cells

as well as supportive glial cells appear to be affected. Patient factors including hyperglycemia, microvascular damage, insulin resistance, and dyslipidemia are thought to contribute to downstream inflammatory signaling, oxidative stress, mitochondrial dysfunction, and ultimately cellular dysfunction and death.

Diabetic peripheral neuropathy carries significant morbidity and mortality.⁵ There is an increased lifetime risk of foot ulceration, Charcot arthropathy, and amputation. Impaired sense of pressure and balance is associated with gait unsteadiness, falls, and bone fractures. Painful neuropathy is associated with mood disorders, sleep disruption, and decreased quality of life—often contributing to decreased work productivity and increased disability. There is also increased risk of hospitalizations and mortality. Annual cost of diabetic peripheral neuropathy and its complications are reported exceed \$10 billion in the United States.⁶

Diabetic peripheral neuropathy is a clinical diagnosis and may be considered a diagnosis of exclusion. There is no single diagnostic gold standard or specific biomarker. The American Diabetes Association recommends that all patients be assessed for diabetic peripheral neuropathy starting at diagnosis for type 2 diabetes and five years after the diagnosis of type 1 diabetes and at least annually thereafter.⁷ This should include symptom assessment, physical examination, consideration of the differential diagnosis, and additional diagnostic studies if needed. A comprehensive diabetic foot examination should include dermatologic, vascular, neurologic, and musculoskeletal/biochemical assessments.⁸ Abnormal sensation using a 10-gram monofilament indicates an increased risk of ulceration. Given time constraints, a 3-minute diabetic foot examination has been proposed.⁹ Diabetes mellitus is common and may occur concurrently with other medical conditions. It is important to identify more treatable and reversible causes of neuropathy. The American Academy of Neurology recommends routinely ordering a comprehensive metabolic panel, a complete blood count, a vitamin B12 level, and serum protein electrophoresis with immunofixation. A referral to neurology can be considered if the presentation is atypical. Various point-of-care diagnostic tests are in development though still need to be validated and demonstrated to be cost effective before widespread use.¹⁰

Randomized controlled clinical trials have consistently demonstrated that achieving near normal glycemic control is important for preventing or delaying progression of peripheral neuropathy in type one diabetes mellitus. This was illustrated in

the DCCT/EDIC trials.¹¹ Intensive glucose lowering therapy during the DCCT significantly reduced the risk of diabetic peripheral neuropathy at trial closure by 64% ($p < 0.01$). The prevalence and incidence of diabetic peripheral neuropathy remained significantly lower in the intensive therapy group through EDIC years 13 and 14. These persistent effects of prior intensive therapy on neuropathy outcomes largely mirror those observed for other diabetic microvascular complications.

It has been more difficult to demonstrate consistent positive impacts of improved glycemic control on neuropathy outcomes in type 2 diabetes mellitus. The ACCORD trial reported a clinically modest but statistically significant risk reduction with the glucose lowering intervention after five years of follow up.¹² A Cochrane systematic review reported rigorous glucose control can decrease the incidence of diabetic peripheral neuropathy in type one diabetes mellitus but has little to no effect in type 2 diabetes mellitus despite more than 10 years of improved glucose control.¹³ This discrepancy highlights the differences between type 1 and type 2 diabetes and also suggests that many people with type 2 diabetes mellitus will develop diabetic peripheral neuropathy despite adequate glucose control.

Potentially contributing factors to this discrepancy include that type 2 diabetes mellitus is commonly associated with insulin resistance, adiposity, and other cardiovascular risk factors. Participants in the BARI 2D trial treated with insulin sensitizing agents had a lower incidence of diabetic peripheral neuropathy over four years than those treated with insulin and/or sulfonylureas.¹⁴ Data from the Look AHEAD trial¹⁵ and the Diabetes Prevention Program¹⁶ suggest that lifestyle interventions that include an exercise component show benefits on peripheral neuropathy outcomes. This suggests that a comprehensive approach utilizing appropriate pharmacologic choices, addressing adiposity and cardiovascular risk factors, and encouraging healthy lifestyle interventions may be more important for patients with type 2 diabetes mellitus than just simply targeting glycemic goals.

To date there are no FDA-approved disease modifying therapies. This appears to be related to limited understanding of the pathophysiological mechanisms. Two agents that have been studied are α -lipoic acid and benfotiamine.

α -lipoic acid, an antioxidant, is commonly used in the management of peripheral neuropathy and is included in some international treatment guidelines. Randomized controlled trials and meta-analyses have shown some improvements in symptom scores and neurological deficits, however, evidence has largely been confined to short-term treatment. The largest trial showed no significant difference in the primary end point between α -lipoic acid treatment and placebo.¹⁷ Benfotiamine, a synthetic derivative of thiamine with improved bioavailability, is thought to inhibit advanced glycation end product production. Small, short duration randomized controlled trials have shown some improvements in symptom scores though larger studies have typically shown no benefit.¹⁸ As such, glycemic control

and lifestyle interventions are the only current options shown to have consistent impact on incidence and progression of diabetic peripheral neuropathy. The effect of glycemic control on the prevention of peripheral neuropathy in type 2 diabetes mellitus is likely quite small, with need for improved disease modifying therapies and other therapeutic options.

Multiple pharmaceutical agents have been approved by the FDA for the treatment of painful diabetic peripheral neuropathy, and multiple treatment guidelines have been published by professional societies to help guide prescribers. In general, anticonvulsants, serotonin and norepinephrine reuptake inhibitors, and tricyclic antidepressants are typically proposed as first line drug therapy. Evidence suggests these options have similar effectiveness. The number needed to treat is considered high, often 3-7, and only 1/3 of patients achieve 50% pain relief. Side effects can be troublesome and there are often low levels of satisfaction associated with these pharmacologic interventions.

Gabapentin and pregabalin are the more commonly used anticonvulsant options. Pregabalin has been specifically approved by the FDA for the treatment of diabetic peripheral neuropathic pain while gabapentin has not. Pregabalin may require less dose titration and has more linear pharmacokinetics compared to gabapentin though it may be more expensive. Adverse events with these medications include somnolence, dizziness, peripheral edema, headache, ataxia, fatigue, xerostomia, and weight gain. A meta-analysis reports the number needed to treat with anticonvulsants is around 7-8.¹⁹

Duloxetine is a serotonin and norepinephrine reuptake inhibitor that has FDA approval for the treatment of diabetic peripheral neuropathic pain. Venlafaxine is another option which has not received specific approval for diabetic peripheral neuropathic pain. Adverse events associated with these medications include nausea, somnolence, dizziness, constipation, dyspepsia, diarrhea, xerostomia, anorexia, headache, diaphoresis, insomnia, fatigue, and decreased libido. A meta-analysis reviewing the effects of serotonin and norepinephrine reuptake inhibitors reports the number to treat of 6.4 (95% CI 5.2-8.4).¹⁹

Tricyclic antidepressants are not specifically FDA approved for the treatment of diabetic peripheral neuropathic pain. Amitriptyline is the best studied and most frequently used tricyclic antidepressant. Nortriptyline and desipramine may have fewer adverse effects and may be safer in older adults. These older agents are the most affordable pharmacologic options. Adverse events include anticholinergic side effects and potential long-term cardiovascular effects. A meta-analysis revealed that the number needed to treat is 3.6 (95% CI 3.0-4.4)¹⁹ though quality of the data in the included studies has been questioned.

Historically there has been few head-to-head comparison studies to guide prescribers to the best first-line treatment. The OPTION-DM trial was published in 2022 and suggested pregabalin, duloxetine, and amitriptyline provided similar pain

relief when used as initial treatment.²⁰ This study also reported that two-drug combinations often provided additional pain relief in patients who had not responded well to monotherapy.

This suggests that if an initial first line therapy is not effective despite appropriate dose titration, one could consider a different first line therapy or a combination of two different first line therapies. If there is still an inadequate response, one should reconsider the diagnosis and consider alternate etiologies. Use of opioid pain medications is no longer routinely recommended for chronic pain though a referral to pain management specialists may be prudent to consider alternative treatment modalities. Two newer treatments are an 8% capsaicin patch and spinal cord stimulation.

An 8% capsaicin dermal patch was approved for the treatment of diabetic peripheral neuropathic pain by the FDA in 2020. Capsaicin reversibly desensitizes the transient receptor potential vanilloid (TRPV1) receptor, which is thought to play an important role in pain signaling. Application of the patch requires trained staff and a suitable clinic infrastructure and may provide long lasting pain relief from a single application. A trial comparing this patch versus placebo suggested that capsaicin patch treatment provides modest improvements in pain and sleep quality over three months.²¹

In 2022, the FDA approved a spinal cord stimulator for the treatment of refractory diabetic peripheral neuropathic pain. In a randomized clinical trial, 10 kHz spinal cord stimulation seemed to safely and effectively treat patients with refractory pain.²²

Other therapies and non-pharmacologic options including 0.075% capsaicin cream, 5% topical lidocaine, transcutaneous electrical nerve stimulation (TENS), and acupuncture. These are not routinely recommended but can be tried despite low levels of evidence. Cognitive behavioral therapy, mindfulness, and structured exercise programs all have limited but promising evidence in management of diabetic peripheral neuropathic pain.²³ For patients with significant neuropathic pain providers should continue to provide appropriate foot care, consider appropriate psychological support and physical therapy.

Diabetic peripheral neuropathy is a common diabetic complication, and its prevalence is expected to increase worldwide as the prevalence of diabetes mellitus increases. Diabetic peripheral neuropathy is and will continue to be an enormous clinical and economic burden. It is important to screen for this condition to detect cases early. For patients with type one diabetes mellitus, there is compelling evidence that targeting near normal glycemic control provides clear and persistent benefits. For patients with type 2 diabetes mellitus, it is likely important to address insulin resistance, adiposity, and cardiovascular risk factors in addition to glycemic control. Unfortunately, there are no reliable effective disease modifying therapies available at this time. There are multiple evidence-based, guideline-recommended medications available for the treatment of painful diabetic peripheral neuropathy, however, these often do

not provide satisfactory relief of symptoms so there is a continued need for more effective agents. Holistic care of the patient with diabetic peripheral neuropathy includes strategies to prevent disease progression, treatment of associated symptoms, and providing appropriate foot care.

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