



## Current And Emerging Insights On Treating Diabetic Peripheral Neuropathy

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*Given the serious consequences of neuropathy for the millions with diabetes, it is vital for physicians to have a full armamentarium of treatment options. These authors detail the finer points of surgical nerve decompression, pharmacologic agents and other emerging treatments.*

Currently, there are 23 million people with diabetes in the United States alone and 50 percent or more will develop peripheral neuropathy.<sup>1</sup> Diabetic peripheral neuropathy continues to be the predisposing factor for diabetic foot complications.<sup>2-4</sup> Even in the presence of underlying vascular disease, neuropathy is the threshold for development of diabetic foot ulcerations. As diabetes mellitus continues its trend toward being a global pandemic, an understanding of diabetic peripheral neuropathy is paramount for the physician treating patients affected by the disease.

In the last eight years the lead author has been involved with the Association of Extremity Nerve Surgeons (AENS), he has gained a wider perspective on the different options available for treating peripheral neuropathy. The lead author has had the pleasure to hear lectures from PhDs in the field of biochemistry who have new insights into the treatment of diabetic neuropathy. The lead author also has heard from pain management specialist MDs from esteemed universities such as Stanford University who have a great grasp of what medications work well and what is just good marketing by the pharmaceutical companies. The lead author has even been exposed to the use of peripheral nerve stimulators that are often a last resort. The lead author also has performed hundreds of decompressions on patients who were diagnosed with nerve entrapment to restore sensation and relieve pain.

Although a complete review of the pathophysiology of diabetic peripheral neuropathy is beyond the scope of this article, the following are the major pathways for the development of neuropathy. They are the polyol, uremic and advanced glycation end product (AGE) pathways.<sup>5</sup> Essentially, they are the result of altered glucose metabolism as a consequence of hyperglycemia. This leads to inhibition of nitric oxide production, accelerated Wallerian degeneration of the nerves and deterioration of the nerve sheath.

Diabetic peripheral neuropathy will present initially with hyperesthesia, defined as “tingling” and hypersensitivity to either temperature or pain, and is followed by painful feelings of burning. The later stages will be defined by anesthesia of the extremities with the feet being affected primarily. All of these manifestations are defined as sensory and primarily affect small nerve fibers.

Diabetic peripheral neuropathy is a progressive and irreversible disease. Physicians direct treatment at addressing euglycemia and symptomatic treatment.<sup>6</sup>

Motor neuropathy is also part of the equation. This will lead to the loss of the motor end plate of the motor nerve fibers, primarily the large nerve fibers. This causes intrinsic muscle atrophy and the classic “intrinsic minus” foot. When this combination is compounded with diminished proprioceptive sensation, it leads to altered gait patterns and abnormal plantar foot pressures that cause stress to the tissues, including skin, ligaments, joint capsules and bones. The results are ulceration, breakdown and finally amputation. Loss of balance also is of consequence.



Peripheral neuropathy is not exclusive to metabolic disease of the nerves. Entrapment of the nerve trunk from hypertrophic deep fascia or muscular structures as well as limb deformity can cause tension or compression on the peripheral nerve. Any trauma including surgery can lead to entrapment. The range of symptoms can go from intermittent paresthesias to the development of drop foot in more severe cases. Patients with peripheral neuropathy will often present with symptoms they describe as burning, tingling, temperature changes and an “electric shock” like feeling down the leg to the foot.

The diagnosis and treatment of small fiber neuropathy has improved and intra-epidermal nerve fiber density testing should be a standard test when assessing neuropathy. In 2010, the European Federation of Neurological Societies and Peripheral Nerve Society decided that the intra-epidermal nerve fiber density test is in fact a reliable and effective measure to assess the progression of small fiber neuropathy although it gives no information on etiology.<sup>6</sup>

This test is a simple 3 mm skin biopsy located 10 cm superior to the lateral malleolus. One then places this into Zamboni’s solution and stains the sample with protein-gene product 9.5. The results often come with a picture of the biopsy under a microscope.

If the test shows a loss of density of these small fibers, it is then likely that the patient will have difficulty with temperature regulation as well as sweat gland problems leading to dry skin and cracking of the skin. Accordingly, it would be important to have the patient apply emollients to the skin on a regular basis. Also, these patients are more likely to benefit from pharmacologic agents as they are less likely to respond to surgery alone.

### **How Effective Is Nerve Decompression For Neuropathy?**

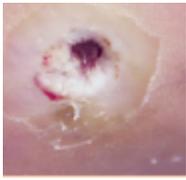
There has been a disconnect between the medical and surgical communities regarding surgical nerve decompression for those with diabetes. When Dellon first published his article on nerve decompression for patients with diagnosed nerve entrapment of the tarsal tunnel, many of the well known, diabetic neuropathy researchers came out strongly against the article and its premise.<sup>7</sup> They tried to paint the procedure as experimental and some even tried to twist the premise of the article, intimating that we surgeons were “curing” diabetic neuropathy. This initial negative connotation to the procedure spread quickly among the academia in the medical community and into the podiatry community.

As a somewhat biased observer of this history and where we are now, the lead author feels they were wrong and remain wrong. Surgeons in the AENS have performed thousands of decompressions on people with and without diabetes with peripheral neuropathy, and have had very high success rates at restoring protective sensation and relieving pain.

Nickerson and colleagues looked retrospectively at patients who had tarsal tunnel decompression and found there was a less than 4 percent ulcer recurrence rate in patients with diabetes.<sup>8</sup>

For any physicians who have not seen the results of these procedures, we would encourage them to explore the large amount of substantive data that is currently available and have an open mind about the possibility for significant improvement for their patients.<sup>9,10</sup> Certainly not all patients with diabetes are candidates for the surgery but we think it would be prudent for all medical professionals to be able to identify those patients who are good candidates and refer them to someone who can perform the surgery.

We feel very comfortable telling our patients that the worst thing that can happen is they just do not see any improvement and it is extremely rare for them to get worse. The lead author notes that probably 85 percent of his patients have improved following surgery, which is consistent with the literature. Along with his other colleagues at AENS, the lead author has personally trained dozens of DPMs to identify and treat patients with peripheral neuropathy.



## Why You Should Consider Nerve Decompression

Even with the currently available research on this procedure, there are still people, especially those in academia, who choose not to recognize that patients with diabetes with a superimposed compression(s) in the lower extremity can benefit from decompression. Carpal tunnel is well documented as an early predictor of diabetes but why is that not accepted in the foot?

It is well documented that a “double crush” syndrome, with diabetes being the first crush and the actual compression being the second crush, exists in the hand and by extension must exist in the ankle and foot.<sup>11</sup>

In his landmark article, Dellon found that decompressing the tarsal tunnel in patients with diabetes not only relieved pain by 80 percent but also restored sensitivity/sensation in the foot.<sup>7</sup> This led to a significantly decreased incidence of new ulcerations in these patients and a decrease in the rate of amputation.<sup>7,12</sup> This has been consistent with our clinical experience.

This does not mean that every patient with diabetic peripheral neuropathy is a candidate for surgical decompression of the tarsal tunnel. One should reserve this surgery only for those patients who have a diagnosed compression of a peripheral nerve in a site of anatomical narrowing. Electrodiagnostic studies carry a false negative rate of 33 percent in people with symptomatic carpal tunnel.<sup>11</sup>

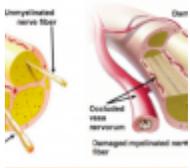
There are no significant systematic reviews of the sensitivity and specificity of nerve conduction velocity (NCV) and electromyography (EMG) in patients with tarsal tunnel syndrome. However, we know we should not rely on these studies to determine whether an entrapment is present as there is a greater than a 50 percent false negative rate with EMG/NCV.<sup>13,14</sup> However, research has shown a positive Tinel’s sign to be a positive predictor of successful surgery in the relief of symptoms in 90 percent of patients with diabetic chronic nerve compression and 88 percent of patients with idiopathic nerve entrapment.<sup>13,14</sup>

We know the changes occurring to the nerve in the tarsal tunnel or any entrapment site manifest in the surrounding connective tissue. Tenosynovitis with accelerated glycosylation and enhanced lysyl oxidase activity result in increased collagen cross-linking, which in turn causes the tissues to become less compliant and even fibrotic. This will subsequently allow shear forces across the nerve to increase and decrease the volume of tissues surrounding the nerve tunnel.

We also know that due to direct damage to the nerve, hyperglycemia leads to apoptosis and impaired mitochondrial function with Schwann cell dysfunction. If we add nerve compression on top of this dysfunction, it is even worse and we can see this microscopically

Furthermore, genetic inheritance can predispose a patient with diabetes to increased sensitivity to compression. This is also the case in hereditary neuropathy with liability to pressure palsy although this is rare. There is also the theory that there is an increased risk of endoneurial hypoxia secondary to a decrease in endoneurial capillary density. Of course, there are other factors, both environmental and biomechanical, that can predispose someone to tarsal tunnel syndrome and other entrapments.

This leads us to patients who come in with complaints of pain in the distal forefoot or cramping in the legs. They may have burning pain and describe temperature abnormalities and interruption of sleep. They often have to wear multiple pairs of socks, even in warmer climates. Getting in the shower is often painful as the hot water can cause allodynia. Some may even describe restless leg syndrome.



In the patient with diabetes, first and foremost you need to make sure that there is optimum glycemic control. It is also important that patients maintain kidney function as well because edema in the leg or foot is a contraindication to surgical intervention. In our practice and in most AENS trained surgeons' offices, we do not rely on EMG/NCV studies to tell us whether the patient has a nerve entrapment. In fact, it is even more difficult to isolate a nerve entrapment in a patient with diabetes using EMG/NCV studies.

## Pertinent Insights On Diagnosing And Treating Nerve Entrapment

Accordingly, we rely on clinical judgment.

Dellon found a statistically significant correlation between a positive Tinel's sign and entrapment of the tibial nerve in the foot.<sup>14</sup> After ascertaining the patient history, perform a methodical neurologic exam, which involves testing all of the muscles and reflexes in the entire lower limb. This takes only a few minutes. Then use a disc discriminator to check two point discrimination on the foot. Then start percussing areas of possible entrapment in the leg. This includes the following nerves and entrapment sites from proximal to distal:

- the common fibular nerve in the fibular tunnel;
- the superficial fibular nerve in the distal aspect of the anterior/lateral leg;
- the deep peroneal nerve in the foot near the base of the second metatarsal;
- the tarsal tunnel at the ankle and distally in the porta pedis; and
- the medial calcaneal nerve in the medial posterior heel region.

After finding an entrapment site, perform a diagnostic block with lidocaine and Decadron to help confirm the diagnosis. If an entrapment is present, as indicated by a positive Tinel's sign and/or a positive provocation sign, one can pursue conservative treatment with neural modulation techniques. This includes sending the patient to a therapist knowledgeable in the art of neural gliding and flossing.

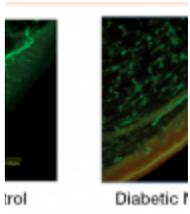
If this is unsuccessful at curing the patient, which is usually the case, then we plan surgery. We almost always perform this surgery on an outpatient basis with the patient having general or spinal anesthesia, or a straight local anesthesia if needed for medical reasons. Surgery involves decompression or external neurolysis of the peripheral nerve(s) in question. These techniques have been honed and improved over the years by our group in the AENS.

The goal is to resect the compressing anatomy that is surrounding the nerve without damaging the nerve itself.

It is important to realize that the underlying anatomy of the peripheral nerves in the legs is quite variable but predictable. It is important to tell the patient that he or she might need further surgery if desired pain relief does not occur. It is imperative that you receive proper training before attempting to perform peripheral nerve surgery. The AENS offers a course once or twice a year.

Instrumentation is also of importance. Bipolar cautery and at least 3.5x loupe magnification is mandatory. One must also realize the importance of exploring all possible areas of potential compression during any surgery. It is also important never to immobilize the foot or leg after surgery as this can lead to scar entrapment and fibrosis.

Now with the advent of new tissue grafts, we will often utilize amniotic based products such as Amniocare™ (Applied Biologics) to avoid any scarring and enhance healing. When necessary, one must be able to perform an internal neurolysis if there is damage to the fascicles. However, in general, it is best to avoid handling of any nerve as much as possible.



Once the surgery is complete, it is important to get the patient ambulating as soon as possible in order to avoid adhesions and excessive scarring to the decompressed nerve. In general, our success rate is around 85 percent for most of the nerves in the lower extremity.

## What You Should Know About Pharmacological Treatment Options

Utilizing topical custom pharmaceuticals plays an important role in the management of neuropathy and newer delivery vehicles are helping get the medication to the specific area needing treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of pain associated with a variety of indications, including arthritic conditions, but their usefulness is often limited by dose-dependent adverse events, such as gastrointestinal disturbances, cardiovascular events and renal toxicity. Topical formulations offer the potential to deliver analgesic concentrations locally at the site of inflammation while minimizing systemic concentrations, which lowers that risk of side effects.<sup>15</sup>

The most commonly used topical medications in the treatment of neuropathy are: gabapentin (Neurontin, Pfizer) ketamine, cyclobenzaprine (Flexeril), amitriptyline (Elavil, Pfizer), fluribiprofen (Ansaid, Pfizer) and ketoprofen (Orudis) along with a local anesthetic such as lidocaine or prilocaine.

Oral medications can play an important role in the successful treatment of diabetic peripheral neuropathy but are not a cure. We have been inundated by pharmaceutical reps who have extolled the virtues of their particular company's drug for the treatment of neuropathy. We are told this is the latest and greatest "super pill." We can all think of a few drugs that we have tried and had high hopes for but ultimately they just made money for the companies without really helping our patients. Before initiating any pharmacologic protocol for your patients, you need to assess them properly, make sure you properly prescribe the drug and monitor its use.

The lead author has seen many patients who are taking gabapentin but not taking it properly. It is a very safe drug and can work well when one administers it properly. Be sure to titrate the drug very slowly. One can give it safely in doses up to 3,200 mg/day or more. The lead author sees too many people taking less than 900 mg a day and they have no relief of symptoms. Then they think the drug does not work. Also, some of them have taken the drug improperly, taking too much too soon and subsequently giving up on the drug because "it did not work."

Amitriptyline is another drug that patients can use but it often has undesirable side effects such as tachycardia and dry mouth. Use this with care in patients with heart disease and depression. However, desipramine, which is in the same class of drugs, has fewer side effects and works just as well if not better in my experience. It is also less expensive than any of the other drugs available. One can prescribe amitriptyline at up to 150 mg/day and ensure titrating the drug up in dosage. The lead author usually uses this as a first-line drug for patients needing pharmacotherapy. The lead author starts at 50 mg/day and increases by 10 to 20 mg every five days or so. You can adjust this to the patient's needs. You will want to check levels of the drug every three months or so to make sure patients are not getting toxic levels. This is rare but it can lead to cardiac problems so you may want to check the electrocardiogram.

Research has shown that topiramate (Topamax, Janssen Pharmaceuticals) can be beneficial in treating small fiber neuropathy as it may help in the regeneration of the small nerve fibers that are damaged with small fiber neuropathy the disease.<sup>16</sup>

Duloxetine (Cymbalta, Eli Lilly) is also a drug that the lead author likes to use. It has shown good efficacy in the treatment of neuropathy but it also has an anti-depression indication. Most people suffering from chronic pain are suffering from depression and we think it is important to address this factor as well.<sup>17</sup> Depression is a very debilitating disease and can affect your whole treatment plan.

One can certainly consider sending the patient to a mental health practitioner. There are support groups available for people suffering from chronic pain. The lead author has seen many patients who were told by other healthcare professionals that they are "crazy" or that they should just live with the pain, and this is very devastating to them.

Fortunately, once the proper diagnosis of a peripheral nerve problem was made, they no longer felt “crazy” and realized they had a physical problem and their depression improved.

Another consideration is to check the hormone levels of your patients. Often, people who have been suffering with chronic pain from neuropathy will have elevated hormones and this sets off a whole cascade of events that are involved in the neurochemistry of pain. The adrenocorticotrophic hormone likely plays a critical role here.

### **Is There Merit To ‘Super Vitamins’?**

Recently, “super vitamins” or nerve nutrient formulation via oral routes have been in widespread use. Specifically, these super vitamins nourish the nerves affected by peripheral neuropathy and allow them to conduct impulses more normally, decreasing symptoms. Almost all of these formulations contain benfotiamine. These formulations are in use worldwide and have had mixed results in easing the symptoms of pain, burning, numbness and tingling in patients with peripheral neuropathy.<sup>18,19</sup>

Benfotiamine has been in use since the early 1960s and has successfully helped tens of thousands of patients suffering from peripheral neuropathy worldwide. It has received widespread study in the scientific literature along with vitamin B derivatives and research has shown that benfotiamine has efficacy in a significant number of patients.<sup>18,19</sup>

### **Does Laser Therapy Have Promise For Neuropathy?**

Cold laser therapy has been around for quite awhile and we are sure many of you reading this have seen demonstrations of these lasers at meetings or even in your office. Most of the data and research of cold laser therapy has occurred in Asia. We have only recently been exposed to its potential benefits and we may only be at the tip of the iceberg regarding the potential benefit to patients.

What is important to know is that all lasers are not created equal and that wavelength is the key to laser treatment. Different wavelengths will treat different things. we are not sure we know what the “perfect” wavelength is to treat diabetic neuropathy. However, a recent study showed that low level lasers can have a positive effect on nerve compression and peripheral neuropathy.<sup>20</sup> Time will tell but we believe cold laser therapy does have a place in our armamentarium in the treatment of neuropathy and we may even combine it with other treatments to provide synergistic results.

### **In Conclusion**

It is safe to say there is no magic wand in the treatment of diabetic peripheral neuropathy. We have a lot of choices and more will surely come along. At the very least, we need to educate ourselves on the various treatment options available to treat the disease and its symptoms. We would encourage all of the readers to learn about peripheral nerve entrapments of the lower extremity and be able to identify them.

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