

## Neuropathy (Diabetic)

Millions of people are living with some form of neuropathy. The term neuropathy means a condition in a nerve or group of nerves that causes pain and dysfunction. There are many different causes of neuropathy and a broad range of symptoms.

Unfortunately, there is no single good treatment for most of the neuropathies, and many neuropathies have no known cause. A number of prescription drugs are used, but all have side effects, and none can actually correct the underlying nerve defect that causes the pain. Nutrient therapy offers a promising alternative for people who want to avoid the side effects of prescription drugs.

Neuropathies can originate either within the central nervous system (these are called central neuropathies, such as Guillain-Barre syndrome), or in the peripheral nerves, which lie outside the central nervous system. These are called peripheral neuropathies and account for the majority of cases. They can have many causes, such as toxins, including alcohol, and metabolic diseases. Diabetes is the cause of the most common peripheral neuropathies.

### WHY NEUROPATHY HURTS

In all forms of neuropathy, there is abnormal stimulation of nerves or damage that results in pain. Peripheral nerves are sensitive conduits that carry impulses from the extremities back to the central nervous system (i.e., the spinal cord and brain). Impulses are transmitted along nerves by changes in the electrical charge of the cell membrane caused by movement of ions such as sodium, potassium, and calcium. Impulses are transmitted between nerves by neurotransmitters such as acetylcholine and substance P, which is responsible for transmitting pain impulses. For protection, most nerves are covered with a thin sheath called myelin, which is made from choline and lipids. The myelin functions like the rubber wrapping around an electrical cord: it insulates the nerve fibers and prevents abnormal transmissions.

Depending on the nature of the specific neuropathy, some part of this system breaks down. In diabetic neuropathy, for example, there is a change in the microvascular network that supplies the nerve with nutrients. This lack of blood supply and nutrients causes the nerve to function abnormally. Diabetic neuropathy tends to occur in more than one nerve area (this condition is called polyneuropathy) and may cause loss of sensation and pain that typically worsens at night. In severe cases, diabetics can suffer from a kind of neuropathy called autonomic neuropathy. In this case, the autonomic nervous system, which controls automatic body functions, is affected with possibly serious consequences, including gastrointestinal problems, bladder-emptying problems, abnormal heart rhythms, and even sudden death (El-Atat FA et al 2004).

Neuropathies can also be caused by specific nutritional deficiencies, such as vitamin B12 deficiency, and infectious diseases such as syphilis.

Pain associated with neuropathy can be very intense and may be described as cutting, stabbing, crushing, burning, shooting, gnawing, or grinding. In some cases, a minimal stimulus such as a light touch can trigger severe pain, or pain may be felt even in the absence of any stimulus. If a problem with the motor nerve has continued over a length of time, muscle shrinkage (atrophy), or lack of muscle tone, may be noticeable.

### OPTIONS FOR TREATING NEUROPATHIES

Unfortunately, treatment options for most neuropathies are less than ideal. The following are some of the common strategies:

- For diabetic neuropathy, blood glucose control is essential because glucose causes high levels of oxidative stress throughout the body. In animals, antioxidant therapy, with glutathione and other antioxidants, has been shown to help prevent neuropathy (Osawa T et al 2005).
- Vitamin B12 deficiency can cause peripheral neuropathies, optic neuropathies, and pernicious anemia. This condition is typically treated with vitamin B12 shots. Additionally, folic acid deficiency has been linked to various neuropathies and is usually treated with supplementation (Sadun AA 2002).
- For neuropathies that are caused by an autoimmune disorder, such as rheumatoid arthritis, lupus, or Guillain-Barre, treatment is generally aimed at the underlying inflammatory condition.
- For neuropathies caused by nerve pressure, treatment focuses on relieving the source of the pressure. This strategy may include ergonomic changes to alter any repetitive motions or positions (such as at a keyboard) that caused the neuropathy, or even surgery to relieve internal pressure. Carpal tunnel syndrome is a common cause of neuropathies in the wrist and hand.

- For neuropathy caused by exposure to toxic metals such as lead or mercury, or to medications, treatment focuses on reducing exposure to the offending substance and reducing blood levels of any toxins. Antioxidants are also frequently used to reduce oxidative stress.

A number of medications may also be prescribed or recommended to help deal with the pain. The most common ones are pain relievers, including over-the-counter medications such as ibuprofen and other nonsteroidal anti-inflammatory drugs. Because of the risk of serious liver and kidney toxicity, Life Extension does not recommend the long-term use of acetaminophen for treatment of neuropathies. Aspirin is also frequently suggested for mild neuropathy.

For more serious neuropathies, drugs such as gabapentin (Neurontin®), carbamazepine (Tegretol®), and phenytoin (Dilantin®) may be prescribed. These drugs were originally developed to treat epilepsy, but they also work to reduce the pain associated with neuropathy. Their main side effect is dizziness. In one study, the combination of gabapentin and B vitamins was shown to effectively and significantly reduce pain and improve quality of life (Medina-Santillan R et al 2004).

Pentoxifylline (PTX) is a prescription drug approved by the US Food and Drug Administration to treat peripheral vascular disease. PTX is prescribed to improve the flow properties of blood by decreasing its viscosity. Aging causes a progressive decline of blood delivery to the tissues. Those who have diabetes experience accelerated circulatory deficit. In a study on diabetic rats, just two weeks of PTX administration resulted in a correction of nerve conduction deficit, amounting to 56.5 percent in the sciatic motor nerve and 69.8 percent in saphenous sensory nerve. PTX restored the microvascular deficit by 50.4 percent (Flint H et al 2000). This study indicates that PTX may be of particular benefit to diabetics, especially those suffering from neuropathy, kidney disease, and other vascular disorders.

Research also suggests that Cytomel®, a drug used to treat hyperthyroidism, is also effective at regenerating damaged peripheral nerves. In animal studies, administration of triiodothyronine, or Cytomel®, can regenerate nerve axons after surgical transection of the sciatic nerve, although the mechanism of action remains unclear (Voria I et al 2006). Researchers believe that triiodothyronine administration may have therapeutic potential in cases of peripheral neuropathy by enhancing nerve regeneration (Schenker M et al 2003).

Finally, antidepressants are sometimes used. These drugs may have side effects that discourage people from continuing their medication, although the side effects tend to be less severe than those of anticonvulsants. Side effects of antidepressants include dry mouth, nausea, tiredness, constipation, and weight gain.

In the most severe cases, opiates such as oxycodone (OxyContin®) may be prescribed. Because of opiates' reputation for dependency, many physicians hesitate to prescribe opiates for pain, even when they are an appropriate therapy. If your physician prescribes opiates, please carefully follow the dosing instructions.

Unfortunately, none of these medications can actually fix the underlying nerve damage. They can only reduce the pain associated with neuropathies.

## NUTRITIONAL OPTIONS FOR NEUROPATHY

If the cause of the neuropathy is known and treatable, then managing the underlying condition is the best option. In many neuropathies, however, no specific cause will ever be identified. In addition, many of the causes of neuropathies are themselves not readily treatable. A number of supplements have been shown to interfere with the underlying mechanisms of a variety of forms of neuropathy.

**Acetyl-L-carnitine.** Acetyl-L-carnitine is known to have neuroprotective properties. Two recent studies have found that acetyl-L-carnitine can limit the neuropathy associated with some chemotherapy drugs (Ghirardi O et al 2005; Maestri A et al 2005).

It has also been shown to limit the neuropathy associated with diabetes. In two randomized, placebo-controlled clinical trials, acetyl-L-carnitine, in daily doses of 500 mg and 1000 mg, was shown to yield significant reductions in pain (Sima AA et al 2005).

In two related studies of diabetic nerve degeneration and neuropathy, acetyl-L-carnitine accelerated nerve regeneration after experimental injury. In the first study, diabetic animals treated with acetyl-L-carnitine maintained near normal nerve conduction velocity without any adverse effects on glucose, insulin, or free fatty acid levels, suggesting that acetyl-L-carnitine can hasten nerve regeneration in the context of diabetes (Soneru IL et al 1997). In another study, carnitine deficiency was shown to correct a number of nerve dysfunctions in animals with chemically induced diabetes (Nakamura J et al 1998).

In a human trial, acetyl-L-carnitine appeared to help prevent or slow cardiac autonomic neuropathy in people with diabetes (Turpeinen AK et al 2000). In a large, multicenter human trial, L-carnitine improved nerve conduction velocity and reduced pain associated with diabetic neuropathy over a one-year period (De Grandis D et al 2002).

**Lipoic acid.** As a powerful antioxidant, lipoic acid positively affects important aspects of diabetes, including prevention, blood sugar control, and the development of long-term complications such as disease of the heart, kidneys, and small blood vessels (Dincer Y et al 2002; Jacob S et al 1995, 1999; Kawabata T et al 1994; Melhem MF et al 2002; Nagamatsu M et al 1995; Song KH et al 2005a; Suzuki YJ et al 1992). It has also been shown to reduce the pain associated with diabetic neuropathy (Halat KM et al 2003). Studies include:

- Clinical trials of people with diabetes who had symptoms caused by nerve damage affecting the heart showed significant improvement taking 800 mg oral alpha-lipoic acid daily without significant side effects (Ziegler D et al 1997a,b).
- In another study, 23 diabetic patients were treated with 600 mg alpha-lipoic acid, delivered intravenously daily for 10 days, followed by 600 mg oral alpha-lipoic acid for 60 days. At the end of the study, all participants showed significant improvements in cranial neuropathy, as well as improvements in both peripheral and autonomic neuropathy, which affects internal organs (Tankova T et al 2005).
- In another study, 26 patients with type 2 diabetes were given 600 mg alpha-lipoic acid daily for 3 months. At the end of the study, 20 patients experienced a significant regression of neuropathic symptoms, while 5 patients experienced a complete cessation of all symptoms. Alpha-lipoic acid was especially beneficial in women and in thinner and younger patients (Negrisanu G et al 1999).

**N-acetylcysteine.** N-acetylcysteine (NAC) is a powerful antioxidant and a precursor to glutathione, an intrinsic antioxidant. Animal studies have shown that NAC can inhibit diabetic neuropathy and protect against neuropathies caused by chemotherapy drugs (Love A et al 1996; Park SA et al 2000).

**Curcumin.** Researchers are continually discovering more benefits from curcumin, which is the yellow pigment that gives turmeric its distinctive golden hue. In a study of inherited peripheral neuropathies, curcumin was shown to relieve neuropathy by causing the release of disease-associated proteins that are produced by a mutated gene (Khajavi M et al 2005). Curcumin has also shown promise in animal studies of diabetic neuropathy and as a neuroprotective agent in central nervous system diseases (Osawa T et al 2005).

**Omega-6 fatty acids.** The body ordinarily makes the gamma linolenic acid (GLA) it needs from linoleic acid, an omega-6 fatty acid found in foods. Among diabetics, however, the body is not able to make sufficient GLA, and it must be supplemented (Cunnane SC et al 1984a,b,c; Horrobin DF 1992a,b; Huang YS et al 1992a,b).

GLA improves diabetic neuropathy if given long enough to work. In one double-blind, placebo-controlled study, 111 people with mild diabetic neuropathy received either 480 mg GLA daily or placebo (Keen H et al 1993). After 12 months, the group taking GLA was doing significantly better than the placebo group. Good results were seen in two smaller studies as well (Cameron NE et al 1998; Jamal GA et al 1990).

**Omega-3 fatty acids.** The omega-3s are found in high quantities in coldwater fish such as salmon and are widely consumed for their anti-inflammatory powers. Omega-3s are essential fatty acids and are important components of cell membranes, including the delicate myelin sheath that protects nerves. Studies have shown that omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are able to reduce demyelination in the nerves of diabetic animals, which reduces neuropathic pain (Gerbi A et al 1999).

**Vitamin B1 (thiamin) and benfotiamine.** Some animal studies have shown a decrease in pain with a combination of vitamin B1, vitamin B6, and vitamin B12 (Franca DS et al 2001; Jurna I 1998; Wang ZB et al 2005). The fat-soluble form of vitamin B1, called benfotiamine, has been used effectively to treat alcoholic and diabetic neuropathies. The most marked pain relief from benfotiamine occurred in patients with diabetic neuropathy after only a three-week trial period (Anisimova EI et al 2001; Haupt E et al 2005; Winkler G et al 1999).

**Vitamin B6.** Vitamin B6 inhibits glycosylation of proteins (Solomon LR et al 1989), one the major risk factors for developing diabetic neuropathy. Diabetes patients with neuropathy have been shown to be deficient in vitamin B6 and to benefit from supplementation (Jones CL et al 1978). Interestingly, the neuropathy caused by vitamin B6 deficiency is indistinguishable from diabetic neuropathy.

**Vitamin B12.** A neuropathy caused by vitamin B12 deficiency is characterized by numbness of the feet, pins-and-needles sensations, or a burning feeling (Davidson S 1954; Sancetta SM et al 1951). Supplementation that restores normal B12 levels is a part of successful treatment of diabetic neuropathy (Bhatt HR et al 1983). In a review of clinical trials conducted between 1954 and 2004, vitamin B12, as well as combination therapy of vitamin B12 and methylcobalamin, was shown to reduce pain (Sun Y et al 2005).

The most common forms of supplemental B12 are cyanocobalamin or hydroxycobalamin. The natural form of B12 found in food is methylcobalamin (or a similar form, adenosylcobalamin). The structure of B12 is very complex, with numerous methyl groups attached. Methyl groups (CH<sub>3</sub>) are used in beneficial methylation reactions, such as those that reduce homocysteine.

Methylcobalamin appears to be the most effective form of vitamin B12 to protect the nerves.

**Vitamin C.** Insulin facilitates the transport of vitamin C into cells, decreasing capillary permeability and improving wound healing. Diabetes depletes intracellular vitamin C, which deprives a diabetic of vitamin C's cellular protection (Sinclair AJ et al 1994). Vitamin C levels have been shown to be reduced in diabetic patients (Ziegler D et al 2004).

**Capsaicin.** Derived from hot peppers, capsaicin has been shown to reduce chronic pain by reducing the stimulation of pain receptors. It is often applied as a cream. Initially, capsaicin may cause a prickly, hot sensation that causes many people to discontinue using it. However, once this first phase passes, capsaicin is effective. It has been documented to reduce the pain associated with diabetic neuropathy without adversely affecting glucose control (Halat KM et al 2003).

**Vitamin E.** Vitamin E is a powerful antioxidant that reduces levels of free radicals and oxidative stress. In a placebo-controlled, double-blind, randomized study of 21 patients with type 2 diabetes, large doses of vitamin E were studied for their ability to reduce neuropathy. During the six-month study, patients were either given placebo or 900 mg vitamin E, then measured for nerve conduction and function. The researchers found that mild to moderate defective nerve conduction was improved with high-dose vitamin E, which suggested that patients with neuropathy might experience a reduction in symptoms (Tutuncu NB et al 1998).

These results appear not to be limited to diabetic neuropathy. In a case study of a 24-year-old man with a progressive disease and peripheral neuropathy, daily supplementation with high-dose vitamin E for two years slowed disease progression and produced significant improvement in his neuropathy (Martinello F et al 1998).

### ***For More Information...***

Additional chapters that might be of interest include:

Diabetes

Chronic Pain

## **ALTERNATIVE THERAPIES FOR NEUROPATHY**

The following nondrug therapies have been shown to reduce the pain associated with neuropathy:

- **Transcutaneous electrical nerve stimulation.** In this therapy, small electrodes placed on the skin deliver tiny electrical impulses to specific nerve pathways. This treatment is effective for some types of pain.
- **Biofeedback.** During biofeedback, people learn how to control body responses to reduce pain. Biofeedback is taught with a special machine in a hospital or medical center. Afterward, patients learn how to control these responses by themselves.
- **Acupuncture.** Acupuncture is a traditional Chinese method of pain relief in which tiny needles are placed in specific spots to relieve tension and stress. Acupuncture has shown specific benefit in treating peripheral diabetic neuropathy (Wang YP et al 2005).
- **Hypnosis.** Hypnosis for pain relief works best on adults who are willing and motivated participants in their own therapy. It must be performed by a qualified professional.
- **Relaxation and visualization techniques.** These exercises range from deep breathing to imaginary "escapes" from the pain. Classes are available through local hospitals and yoga centers to help people learn how to control their pain in this way.

## **LIFE EXTENSION FOUNDATION RECOMMENDATIONS**

Whether or not the cause of neuropathy is known, it can be a debilitating condition that seriously impacts quality of life. If the cause is known, the first strategy should be to address the underlying condition. If the neuropathy is caused by alcohol, cocaine, medication, or environmental toxins, exposure to those agents should be limited if possible. Do not discontinue prescription medications without permission from your physician, but inquire whether it may be possible to find a substitute therapy for a neuropathy-causing drug. In the event the neuropathy is caused by heavy metals, such as mercury or lead, chelation therapy may be useful. In addition, administration of Cytomel®, a synthetic thyroid hormone, may boost peripheral nerve regeneration. Before taking Cytomel®, have your thyroid hormone levels tested.

Because diabetes is a common cause of peripheral neuropathy, diabetics are strongly encouraged to read the chapter Diabetes in this book. Strict glucose control is very important, and diabetics must be aware that any substance ingested may affect their blood sugar levels.

The following supplements have been shown to reduce the pain associated with neuropathy:

- **Fat-soluble vitamin B1 (benfotiamine)**—150 milligrams (mg) one to three times daily
- **Acetyl-L-carnitine**—2000 mg daily
- **R-lipoic acid**—300 to 450 mg daily (or alpha-lipoic acid: 600 to 1000 mg daily)
- **NAC**—600 mg daily
- **Curcumin**—800 to 1600 mg daily
- **Gamma linolenic acid (GLA)**—900 to 2700 mg daily
- **EPA/DHA**—4000 mg daily, providing at least 1400 mg EPA and 1000 mg DHA
- **Vitamin B6**—100 mg daily
- **Vitamin B12**—1000 micrograms (mcg) of the methylcobalamin form, taken one to four times daily (up to 40 mg daily methylcobalamin may be used in extreme cases)
- **Vitamin C**—about 2500 mg daily
- **Vitamin E**—400 international units (IU) daily (with around 200 mg gamma tocopherol)

## **NEUROPATHY (DIABETIC) SAFETY CAVEATS**

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### **Acetyl-L-Carnitine**

- Acetyl-L-carnitine can cause gastrointestinal symptoms such as nausea and diarrhea.

### **Curcumin**

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

### **EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

### **GLA**

- Consult your doctor before taking GLA if you take warfarin (Coumadin). Taking GLA with warfarin may increase the risk of bleeding.
- Discontinue using GLA 2 weeks before any surgical procedure.
- GLA can cause gastrointestinal symptoms such as nausea and diarrhea.

### **Lipoic Acid**

- Consult your doctor before taking lipoic acid if you have diabetes and glucose intolerance. Monitor your blood glucose level frequently. Lipoic acid may lower blood glucose levels.

### **NAC**

- NAC clearance is reduced in people who have chronic liver disease.

- Do not take NAC if you have a history of kidney stones (particularly cystine stones).
- NAC can produce a false-positive result in the nitroprusside test for ketone bodies used to detect diabetes.
- Consult your doctor before taking NAC if you have a history of peptic ulcer disease. Mucolytic agents may disrupt the gastric mucosal barrier.
- NAC can cause headache (especially when used along with nitrates) and gastrointestinal symptoms such as nausea and diarrhea.

### **Vitamin B1 (Thiamin)**

- Individuals who are being treated with levodopa without taking carbidopa at the same time should avoid doses of 5 milligrams or greater daily of vitamin B6.

### **Vitamin B6**

- Individuals who are being treated with levodopa without taking carbidopa at the same time should avoid doses of 5 milligrams or greater daily of vitamin B6.

### **Vitamin B12 (cyanocobalamin)**

- Do not take cyanocobalamin if you have Leber's optic atrophy.

### **Vitamin C**

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

### **Vitamin E**

- Consult your doctor before taking vitamin E if you take warfarin (Coumadin).
- Consult your doctor before taking high doses of vitamin E if you have a vitamin K deficiency or a history of liver failure.
- Consult your doctor before taking vitamin E if you have a history of any bleeding disorder such as peptic ulcers, hemorrhagic stroke, or hemophilia.
- Discontinue using vitamin E 1 month before any surgical procedure.

For more information see the Safety Appendix

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