



Diabetes Watch:

Nutritional Compounds: Can They Have An Impact With Diabetic Neuropathy?

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Diabetic neuropathies are a consequence of long-term hyperglycemia and occur in patients with type 2 diabetes, usually those who are 40 years of age or older. Diabetic neuropathy may occur regardless of whether a patient has insulin-dependent or non-insulin dependent diabetes.

Bear in mind that diabetic neuropathy may have a variety of clinical characteristics. Patients may have a symmetric or asymmetric presentation. They may have sensory or autonomic neuropathy. You may note a mononeuropathic or polyneuropathic presentation. Some patients may have entrapment neuropathies while others do not.

Many patients have mixed varieties of neuropathy involving the sensory nerves of the distal limbs and the autonomic nervous system. Many of the sensory neuropathies involve pain and patients frequently describe the pain as burning and numbness. These symptoms interfere with sleep, daily activities and quality of life.

Researchers have proposed many theories to explain the chronic complications of diabetes mellitus (DM). The first is that a high level of intracellular glucose leads to nonenzymatic glycosylation of protein molecules from the interaction of glucose with amino groups, forming advanced glycosylation end products (AGEs). The second hypothesis is that chronic high levels of glucose result in excessive metabolism via the sorbitol pathway.

A third theory is that hyperglycemia increases oxidative stress and free radical generation. One study examined this hypothesis by evaluating the effect of alpha-tocopherol depletion in normal and streptozotocin-induced diabetic rats with peripheral nerve neuropathy. Authors say their data "highlight the importance of reactive oxygen species in the etiology of impaired nerve maturation and regeneration in experimental diabetes, and indirectly support the view that antioxidant treatment could have a therapeutic role in patients."¹

While the treatment of diabetic neuropathy has improved with the application of antiepileptic drugs and antidepressants, it still remains frustrating. Most of the commonly used medications have anticholinergic side effects or cause sedation. They also only treat the symptoms and not the underlying cause of the neuropathy.

With this in mind, we conducted a study to determine if we could improve patients' reports of pain and numbness by utilizing nutritional supplements that may partially address the causes of diabetic complications.

A Closer Look At The Study

We selected one supplement with five nutritional compounds on the basis of their activity and application to the aforementioned theories of diabetic complications.

NeuropathyRX (Neuropathy Solutions) contains N-acetyl-cysteine (NAC), alpha-lipoic-acid (ALA), L-carnitine (LCA), vitamin C and selenium. N-acetyl-cysteine is a reducing agent, a potent antioxidant and serves as a major precursor to the antioxidant glutathione. It also protects the kidneys from contrast-induced nephropathy.² Glutathione also appears to reverse the early effects of glycosylation and subsequently the formation of AGEs.³

Alpha-lipoic-acid is a potent antioxidant involved in metabolic reactions in the mitochondria and energy production. In animal models of diabetes, it reverses the decrease in nerve blood flow.⁴ L-carnitine helps correct elevated sorbitol levels in rat models of diabetes.⁵ Selenium is a potent antioxidant that works synergistically with vitamin E. Vitamin C is the most important water-soluble antioxidant. It scavenges both nitrogen and oxygen reactive species. It may also have a beneficial effect on the production of sorbitol and its metabolites in the hyperglycemic state.⁶

This was an open-label study. We selected patients from a practice of podiatrists. We enrolled patients who complained of neuropathy symptoms despite maximum medical therapy. Out of the 30 patients who enrolled, 28 completed the six-month study. The average age was 68 with an age range from 48 to 94. Twelve patients were men and 16 patients were women. Most patients had comorbid conditions including hypertension, obesity and hyperlipidemia.

Researchers asked patients to rate eight parameters using a modification of the Wong-Baker FACES Pain Rating Scale. The eight parameters were:

- Burning pain
- Numbness
- Overall pain
- Perceived level of impairment of function
- Perceived level of impairment of concentration
- Perceived level of impairment of thought clarity
- Perceived level of impairment of alertness
- Perceived level of impairment of energy

The last four parameters were secondary endpoints that we assessed because an earlier pilot investigation indicated the nutritional supplements had a salutary effect on mental function. We followed the patients for three months. We conducted the pain ratings at the initiation of the study and every four weeks thereafter (see “How One Nutritional Supplement Affected Neuropathy-Related Pain And Impairment” above).

What The Study Reveals About Nutritional Compounds And Diabetic Neuropathy

We began our investigations with the assumption that while over-consumption of fats and carbohydrates contributes to diabetes, the under-consumption of critical micronutrients leads to the complications. In designing which nutrients to replenish, we assumed multiple factors are missing from the average diet in patients with diabetic neuropathy.

We then chose nutritional supplements that would address the major theories of diabetic complications. Four compounds also intersect in maintaining levels of intracellular reduced glutathione (GSH).

Cysteine availability most often limits GSH biosynthesis in vivo. One orally bioavailable cysteine source is N-acetylcysteine (NAC). The antioxidant ALA is also important in replenishing GSH. Oral ALA raises GSH levels in HIV patients and is extremely safe and well tolerated. Ascorbate conserves intracellular glutathione and probably is a redox GSH co-factor.⁷ Selenium is an important component of the enzyme glutathione peroxidase that works with glutathione to reduce free radicals.

Glutathione is a tripeptide intracellular thiol molecule derived from glycine, L-glutamine and L-cysteine. Intracellular reduced glutathione is an extremely important cell protectant. It is a potent antioxidant and enzyme cofactor, and its depletion by the absence of dietary precursors results in cell death. It directly quenches reactive hydroxyl free radicals, oxygen free radicals and biomolecules.⁸ Intracellular reduced glutathione balance is crucial to intracellular homeostasis. It stabilizes the cellular biomolecular spectrum and facilitates cellular performance and survival. Individuals with inherited deficiencies of the GSH develop hemolytic anemia, spinocerebellar degeneration and peripheral neuropathy along with other manifestations.⁹

Individuals with impaired glucose tolerance, including those with early hyperglycemia, have reduced blood GSH and, as discussed above, this increases the formation of AGEs.¹⁰

In Conclusion

While over-consumption of the macronutrients, carbohydrates and fats can lead to obesity and diabetes, it is less obvious that under-consumption of key micronutrients can lead to diabetic complications including neuropathy. This investigation indicates that certain nutrients can alleviate the complaints of burning and pain that accompany diabetic neuropathy.

It would also suggest that other critical supplements like omega 3 fatty acids may be lacking from the diets of patients with diabetes and their absence could also contribute to diabetic complications. In the future, it may be beneficial to counsel those with diabetes to include key nutrients in their diet as well as watching their calories.

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Editor's note: For related articles, see “A Guide To Nutritional Supplements For Patients With Diabetes” in the March 2006 issue or “Current And Emerging Options In Treating Diabetic Neuropathy” in the March 2005 issue. For other related articles, visit the archives at www.podiatrytoday.com.