

Relief of Symptoms Associated with Peripheral Neuropathy

Low-level consumption of glutathione-enhancing micronutrients may be beneficial in relieving symptoms of neuropathy of unknown origin.

By Mark Gostine, MD and Larry Pawl, MD



The diseases causing polyneuropathy (PN) are myriad and complex.

PN can result from metabolic and systemic insults including diabetes, liver and renal failure, vitamin B12 deficiency, collagen vascular and immune disorders like Guillain-Barre, hypothyroidism, malabsorption from celiac sprue, the remote effects of carcinoma, multiple myeloma, lymphoma, Lyme disease, HIV, and monoclonal gammopathy. Toxins can also cause PN; the most prominent are acrylamide, arsenic, diphtheria, lead, organophosphates and thallium. Many antineoplastic agents result in damage to the peripheral nerves including taxanes, vincristine, cisplatin and other drugs like amiodarone, disulfiram, metronidazole, phenytoin and megadoses of pyridoxine. Lastly, PN is common in inflammatory vascular disorders appearing in half the cases of polyarteritis nodosa and inherited peripheral nerve diseases such as Charcot-Marie-Tooth.

The classification of peripheral neuropathy has become increasingly complex as the capacity to discriminate new subgroups and identify new associa-

tions with toxins and systemic disorders improves. Our grasp of the pathophysiologic basis of the clinical PN has increased rapidly, but these advances are primarily descriptive and little progress has been made in understanding the fundamental pathogenic events that underlie the polyneuropathies.

While the treatment of peripheral neuropathy has improved with the use of antiepileptic drugs and antidepressants, it still remains frustrating. Most of the commonly used medications have anticholinergic side effects or cause sedation. At best, they are only partially effective because they do not treat the underlying cause of the neuropathy but only the symptoms.

Recognizing the limitations of pharmaceutical treatment, we previously reported on the therapeutic application of a combination of five micronutrients for management of diabetic neuropathy¹:

1. alpha-lipoic acid
2. n-acetyl-cysteine
3. L-carnitine
4. selenium
5. vitamin C

Throughout the course of our investigations it became apparent that patients with peripheral neuropathy of unknown origin seemed to benefit from the use of these agents as well. This prompted an extension of our original efforts. We conducted an open label study of patients with peripheral neuropathy of multiple etiologies. It is conceivable that the supplements we used benefit peripheral nerves—regardless of the cause of the neuropathy—because they increase the intracellular ratio of glutathione from its reduced to oxidized form.

About Glutathione (GSH)

The activities of the above five micronutrients intersect at glutathione. Glutathione (GSH) is a tripeptide intracellular thiol molecule derived from glycine, L-glutamine and L-cysteine. GSH is an extremely important cell protectant. It is a potent antioxidant and enzyme cofactor whose depletion—by the absence of dietary precursors—results in cell death. It directly quenches reactive hydroxyl free radicals, oxygen free radicals, and biomolecules.² GSH balance is crucial to intracel-

lular homeostasis, stabilizing the cellular biomolecular spectrum, and facilitating cellular performance and survival. Individuals with inherited deficiencies of the GSH develop hemolytic anemia, spinocerebellar degeneration, and peripheral neuropathy, along with other manifestations. Glutathione-S-transferase (GST), through its inter-actions with GSH, reduces the manifestations of neuropathy in individuals with Charcot-Marie-Tooth disease.³ GST genotypes impact the expression of peripheral neuropathy secondary to taxanes toxicity.⁴

As a tripeptide, GSH does not survive digestion. Therefore merely consuming GSH will not raise blood levels. The micronutrients used in our study population all impact either the synthesis of GSH or reconstitute reduced GSH from its oxidized state.

N-acetyl-cysteine (NAC) is a reducing agent, a potent antioxidant and an important source of cysteine, the rate-limiting major precursor to the antioxidant glutathione. It is through this mechanism that it protects the liver from overdoses of acetaminophen. It protects the kidneys from contrast-induced nephropathy⁵ and prevents arsenic-induced neurotoxicity by replenishing GSH.⁶

Alpha-lipoic-acid (ALA) is a potent antioxidant involved in metabolic reactions in the mitochondria and a cofactor in energy production. In animal models of neuropathy, it reverses the decrease in nerve blood flow.⁷ ALA is vital for reconstituting reduced GSH after it has neutralized free radicals.

L-carnitine (LCA) is a vitamin-like compound that serves as a carrier to transport long-chain fatty acids into the mitochondria for beta-oxidation. Its depletion in rats significantly reduces intracellular GSH and increases toxicity from exposure to carboplatin.⁸

Vitamin C is the most important water-soluble antioxidant. Adequate vitamin C increases GSH levels in red blood cells. Ascorbate conserves intracellular glutathione and probably is a redox GSH cofactor.⁹ Conversely, GSH and GSH enzymes reconstitute vitamin C after it has neutralized a free radical.

Selenium is a potent antioxidant that works synergistically with vitamin E. It is an important component of the enzyme glutathione peroxidase that works with glutathione to reduce free radicals.

TABLE 1. Study Results Over 9 Months—Percent Reduction in Pain

	3 months	5 months	7 months	9 months
Overall pain	47	67	65	67
Burning pain	54	71	74	70
Numbness	44	65	59	66

Study Population

Forty-three patients with documented peripheral neuropathy were recruited for the open label study. All study participants gave their informed signed consent and followed an interventional protocol. There were 28 females and 15 males whose age ranged from 43 to 91 and averaged 69. The duration of their neuropathy ranged from 2 to 15 years. Patients had all failed therapy consisting of antiseizure and antidepressant medications. There were 26 diabetics in the study and the rest had no known etiology and were labeled as neuropathy of unknown origin. Most patients had comorbid conditions including hypertension, obesity and hyperlipidemia.

Methods

The participants were followed for nine months and were assessed using modified Wong-Baker FACES pain rating scale to include numbness, overall pain and burning pain to test for correlation in response. Assessments were made at three, five, seven and nine months. Results are reported as percent improvement in all three measures at each marking period in the table below.

Study Results

Examining Table 1, it is apparent there were significant reductions in the primary endpoints of burning, numbness, and overall pain. The most dramatic improvement was in burning pain. These results are consistent with our original findings and extend that study by increasing the number of patients and monitoring them for a longer period of time. Further, almost half the patients in this study had neuropathy of unknown origin as compared to the first study of patients with diabetic neuropathy.

Discussion

Many neurologic diseases are characterized by damage consistent with excessive

oxidative stress and elevated levels of free radicals. Glutathione levels are clearly depressed in Parkinson's disease and may be linked to progression of neurologic deterioration.¹⁰ Research by Ortiz¹¹ has shown higher levels of oxidative metabolites in the serum of MS patients. In the peripheral nervous system, antioxidants attenuate oxidative stress and the inflammatory cascade in diabetic and alcoholic neuropathy.¹² Oxidative stress also seems to play a prominent role in neuropathy associated with taxane toxicity and chemotherapy.¹³ From these observations and others, we can conclude that glutathione is a common and critical defense against a multitude of neurological insults.

Glutathione is the most important thiol-containing peptide involved in detoxification—not only in the human body but across the animal kingdom including vertebrates and invertebrates. It is present in high concentrations in the liver and kidneys, the organs responsible for eliminating toxins from the body. It is also present, in substantial levels, in the nervous system where it is a primary defense against oxidative stress including mercury and other heavy metal toxicity. As a potent and ubiquitous antioxidant, it appears logical that increasing its precursors and cofactors would yield substantial benefit to peripheral neuropathy given that many forms of neurodegeneration share the common denominator of increased free radical production.

Conclusion

In our previous open label study of diabetics with neuropathy we concluded that while *abuse* of macronutrients causes type 2 diabetes, the low consumption of critical micronutrients may be beneficial in relieving symptoms of peripheral neuropathy. Given the wide myriad of insults that can result in neuropathy of known causes, it would appear the same reasoning may apply even to neuropathy (*Peripheral Neuropathy continued on page 49.*)

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of unknown origin. The human body maintains homeostasis until it reaches a tipping point. Maintaining the proper ratio of reduced glutathione to oxidized glutathione within cells can help forestall the tipping point that results in nerve disorders. After having conducted two open label studies and confirming results, further testing with a double blind study would appear to be indicated. ■

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