

# DIABETIC NEUROPATHY STUDY

Under-consumption or lack of critical nutrients in the diets of diabetics may be implicated in diabetic complications, including neuropathy.

By Mark Gostine, MD; Larry Pawl, MD;  
Michael David, DPM; and William Decker, DPM



Diabetic neuropathies are a consequence of long term hyperglycemia and occur whether the diabetes is insulin dependent or not. In patients with juvenile diabetes, these problems arise in the third through fifth decade and, in type two diabetes, usually after the fifth decade of life. Focal mononeuropathies can cause third and sixth cranial nerve palsies, painful intercostal neuropathy, and isolated muscle weakness involving the hip girdle. These mononeuropathies are likely vascular in origin and usually resolve over a period of months. While the distal symmetrical neuropathies may have an element of ischemia, they most likely represent a confluence of metabolic disturbances.

There are multiple characteristics used to classify diabetic neuropathy including whether they are symmetric or asymmetric, sensory or autonomic, mononeuropathy or polyneuropathy, and entrapment neuropathy or not. Many patients have mixed varieties of neuropathy involving the sensory nerves of the distal limbs and the autonomic nervous system. Autonomic neuropathies can result in disturbances of gastrointestinal, sexual, and vasomotor functions. Many of the sensory neuropathies involve pain which is frequently described as burning and numbness. These symptoms interfere with sleep, daily activities, and quality of life.

While the treatment of diabetic 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. The goal of this study was to determine if we could improve patients' reports of pain and numbness with the utilization of nutritional supplements that may partially address the causes of diabetic complications.

## Mechanism of Action

Many theories have been proposed 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 and thus forming advanced glycosylation end products (AGEs). AGEs result in numerous deleterious consequences including glomerular dysfunction, acceleration of atherosclerosis, dysfunction of endothelium, reduction of nitric oxide synthesis, and alteration of extracellular matrix.

**Table 1. Ratings of Parameters Over the 3 Month Study at 4-week Intervals.**

	Initiation	4 weeks	8 weeks	12 weeks	% change 4 weeks	% change 8 weeks	% change 12 weeks
Burning	6.59	4.71	3.06	2.44	-29%	-54%	-63%
Numbness	7.41	6.21	5.16	4.37	-16%	-30%	-41%
Overall pain	6.54	4.98	3.67	2.85	-24%	-44%	-56%
Impairment of function	4.3	3.93	2.96	2.76	-9%	-31%	-36%
Impairment concentration	3.11	2.91	2.33	2.26	-6%	-25%	-27%
Impairment clarity	2.18	2	1.78	1.74	-8%	-18%	-20%
Impairment alertness	2.39	2.2	1.69	1.52	-8%	-30%	-36%
Impairment energy	4.89	4.29	3.61	3.33	-12%	-26%	-32%

The second hypothesis is that chronic high levels of glucose result in excessive metabolism via the sorbitol pathway. Normally glucose is metabolized via glycolysis after phosphorylation. When the cell is confronted with high levels of glucose and the normal metabolic pathway is saturated, sorbitol levels increase via the enzyme aldose reductase resulting in altered intracellular redox potential.

A third theory is that hyperglycemia increases oxidative stress and free radical generation. This hypothesis is supported by evaluating the effect of alpha-tocopherol depletion in normal and streptozotocin-induced diabetic rats with peripheral nerve neuropathy.<sup>1</sup>

### Selection of Supplemental Nutrients

In designing which nutrients to replenish, the authors assumed multiple factors are missing from the average American diet that which may be adversely impacting patients with diabetic neuropathy. Five nutritional supplements, dubbed NeuropathyRX, were chosen on the basis of their activity and application to the theories of diabetic complications enumerated above. NeuropathyRX contains N-acetyl-cysteine (NAC), alpha-lipoic-acid (ALA), L-carnitine (LCA), vitamin C, and selenium.

**N-acetyl-cysteine (NAC)** is a reducing agent, a potent antioxidant and serves as a major precursor to the antioxidant glutathione. It is through this mechanism that it protects the liver from overdoses of acetaminophen. It also protects the kidneys from contrast-induced nephropathy.<sup>2</sup> Glutathione also appears to reverse the early effects of glycosylation and therefore the formation of AGEs.<sup>3</sup>

**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 diabetes, it reverses the decrease in nerve blood flow.<sup>4</sup>

**L-carnitine (LCA)** helps correct elevated sorbitol levels in rat models of diabetes.<sup>5</sup>

**Vitamin C.** It can be argued that 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.<sup>6</sup>

**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.

Four of the 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 alpha-lipoic acid (ALA) is also important in replenishing GSH. Orally, it raises GSH levels in HIV patients and is extremely safe and well tolerated. Ascorbate conserves intracellular glutathione and probably is a redox GSH cofactor.<sup>7</sup>

Glutathione 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.<sup>8</sup> GSH balance is crucial to intracellular homeostasis, stabilizing the cellular biomolecular spectrum, and facilitating cellular performance and survival.

Individuals with inherited deficiencies of the GSH develop hemolytic anemia, spinocerebellar degeneration, peripheral neuropathy, along with other manifestations.<sup>9</sup> Individuals with impaired glucose tolerance, including early hyperglycemics, have reduced blood GSH<sup>10</sup> and, as noted above, increases the formation of AGEs.

## Study Population

This was an open label study. Patients enrolled were selected from a practice of podiatrists specializing in surgical and non-surgical care of the feet and ankles. The nature of their practice results in a large population of patients suffering from complications of the diabetic foot including ulcers, infections, calluses and neuropathy. Patients complaining of symptoms of neuropathy, despite maximal medical therapy, were entered in the study investigating the use of nutritional supplements for control of pain. Thirty patients were enrolled and 28 completed the study over a six month period extending from November of 2006 through May of 2007, with twelve men and sixteen women participating. The average age was 68 with a range from 48 to 94. Most patients had comorbid conditions including hypertension, obesity and hyperlipidemia.

## Methods

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

1. Burning pain
2. Numbness
3. Overall pain
4. Perceived level of impairment of function
5. Perceived level of impairment of concentration
6. Perceived level of impairment of thought clarity
7. Perceived level of impairment of alertness
8. Perceived level of impairment of energy

The last four parameters were secondary endpoints that we assessed because an earlier pilot investigation indicated that nutritional supplements had a salutary effect on mental function. Patients were followed for three months with ratings at initiation and every four weeks thereafter.

## Results

Examining Table 1, it is apparent there were significant reductions in the primary endpoints of burning, numbness, and overall pain. There were also significant reductions in impairment of mental function, although not to the same degree. Interestingly, every parameter improved at every assessment, suggesting that had the patients been studied for a longer period of time, the study may have recorded further improvement. The most dramatic improvement was in burning pain. Many patients requested to remain on the supplement after the study ended due significant reductions in their pain.

## Discussion

The investigation was started with the assumption that, while over-consumption of fats and carbohydrates contribute to diabetes, the under-consumption of critical micronutrients leads to the complications. Mankind's dietary habits evolved during the Paleolithic period which extended from 2.5 million years ago until the development of agriculture about 10,000 years ago. Recent reports out of Lund University in Sweden reveal that a Paleolithic diet was superior to a Mediterranean diet in controlling type 2 diabetes.<sup>11</sup> This diet consisted of fruits, vegetables, lean meats, nuts, seeds, and contained low levels of refined sugars and carbohydrates. It also included high levels of beneficial micronutrients including omega 3 fatty acids, bioflavonoids, minerals, vitamins, and anti-oxidants.

The Western diet, on the other hand, is high in refined sugar and fats and is a phenomena of the last two generations. There has been no time at all for evolutionary selection to compensate for the rapid change in such eating habits. While most authorities are in agreement about the hazards of over-consumption of the wrong types of foods, there is less agreement on the problems associated with the under-consumption or absence of health-promoting micronutrients.

*“The most dramatic improvement was in burning pain. Many patients requested to remain on the supplement after the study ended due significant reductions in their pain.”*

## 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 a combination of certain nutrients can alleviate the complaints of burning and pain that accompany diabetic neuropathy. It would also suggest that other critical nutrients may be lacking from diets of diabetics and their absence could also contribute to diabetic complications. In the future, it would appear from our findings that it would be beneficial to counsel diabetics to include key nutrients in their diet as well as watch their calories. ■

*Mark Gostine, MD is a pain management physician and president of Michigan Pain Consultants.*

*Larry Paul, MD is an oncologist in Grand Rapids, Michigan.*

*Drs. Michael David and William Decker are podiatrists and directors of Foot and Ankle Specialist of West Michigan.*

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