

Nitric Oxide and Its Role in Health and Diabetes.

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Part 8. Nitric Oxide(NO) and diabetic peripheral neuropathy (DPN)

Diabetic Peripheral Neuropathy (DPN; peripheral nerve damage) is a common complication of diabetes. Almost 70% of people with diabetes develop DPN within 5 years and after 5 years the incidence rate increases to almost 100%. DPN most often begins as a tingling feeling and insidiously progresses to loss of sensation to hot and cold and to pressure. Additionally, DPN sometimes manifests itself as diffuse pain in the extremities. DPN is uncomfortable, may lead to poor balance and higher risks of falls, and is dangerous to those who have it. We have all come in contact with people with insensate feet who have developed ulcers because they did not sense poorly fitting shoes or unexpected foreign objects.

Recently, the Centers for Medicare and Medicaid Services (formerly HCFA) in Decision Memorandum CAG 00059 characterized DPN with loss of protective sensation (LOPS) as a localized illness of the foot and the most important factor leading to amputation in people with diabetes. Diagnostically, this Decision Memorandum states that DPN with LOPS is determined by insensitivity to a Semmes Weinstein 5.07 Monofilament at 2 sites on the bottom of the foot.

Just how does DPN occur in people with diabetes? The causation is debated among researchers and clinicians in the field. One theory is that progressive loss of circulation to the peripheral nerves is the cause of DPN. Another theory is that DPN is due to nerve dysfunction possibly due to accumulation of sorbitol on peripheral nerves. According to the NIDDK (Peripheral Neuropathy: The Nerve Damage of Diabetes), other researchers believe that lack of nitric oxide or poor nitric oxide metabolism may be the culprit. The debate and research goes on and hopefully one day we will have the answer.

While the pain associated with DPN may respond to drug therapy (for instance, Neurontin) or to topicals (lidocaine or capsaicin), clinicians have had little in their armamentarium to reverse the progressive loss of sensation observed with DPN. Clinical trials for a class of drugs known as aldose reductase inhibitors have been unsuccessful. However, Dellon has reported success with a surgical intervention similar to that employed in carpal tunnel release. Additionally, alpha lipoic acid is under investigation in Europe as having potential to increase sensation in cases of DPN.

The American Diabetes Association, based on the 10-year study of 1,441 patients with IDDM, recommends, that tight glucose control is one of the best ways to delay the onset or progression of DPN. Tight glucose control may delay the onset of LOPS in DPN, by

decreasing the accumulation of sugar molecules called sorbitol within the nerves themselves. Reducing serum glucose levels also lowers the concentration of glycosylated hemoglobin (HbA1c). We have already mentioned in an earlier article that people with diabetes produce lower than normal levels of nitric oxide that may account for decreases in blood flow and a decreased capacity of blood vessels to dilate. Now we know that even the low amounts of NO produced are tightly bound to glycosylated hemoglobin. Not surprisingly, when HbA1c is elevated, the NO that is present in red blood cells is not easily released to promote vasodilation. This may account, in part, for very low blood flow to the nerves of the feet and, thus to the symptoms of DPN.

In view of the risks associated with DPN, either slowing its progression or, hopefully, reversing its course, is a worthwhile clinical goal. A promising new approach involves the use of an FDA cleared, non-invasive, medical device which may increase local levels of NO, thereby restoring circulation to the feet of people with DPN. It is hypothesized that that this device may promote a NO-mediated increase in circulation to help to regrow nerves that were lost to DPN or it may reestablish normal function in those nerves that still remain in the feet, or both. The first report (A Kochman, et. al., JAPMA 2002, in press) of the effect of this drug-free technology on patients with DPN is very encouraging. After only one month of treatment (3X/week for 30 min/day), 42/42 patients who were insensate to a Semmes Weinstein 5.07 Monofilament when they entered the study were able to feel this 5.07 Monofilament at the conclusion of the study. In other words, loss of protective sensation was no longer clinically present.

The next article will detail why this device, the Anodyne Ò Therapy System, may be able to alter local levels of nitric oxide so as to restore sensation lost with diabetes.

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