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# Exploring the Role of Metanx® in Diabetic Neuropathy

INTRODUCTION AND COMMENTARY BY AARON I. VINIK, MD, PHD, AND VIVIAN FONSECA, MD

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# Exploring the Role of Metanx® in Diabetic Neuropathy

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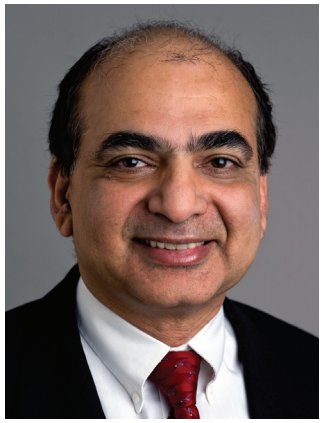

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## Prevalence and Etiology

Diabetic neuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes, after the exclusion of other causes.[1,2] It is a common complication of diabetes, occurring about equally among patients with type 1 or type 2 diabetes, and is a significant source of morbidity and mortality.[3] One of the most serious morbidities is foot ulceration, which can lead to gangrene and limb loss; diabetic neuropathy is responsible for 50% to 75% of nontraumatic amputations in developed countries.[1]

Prevalence measurements vary widely due to differences in defining diabetic neuropathy, the tests used to assess neuropathy, and the type of patient populations studied.[4] Although the true prevalence of diabetic neuropathy is unknown, data suggest that at least half of diabetic patients have symptoms of neuropathy.[5] It has been suggested that neuropathic complications may begin even before the full clinical diagnosis of diabetes, since about 11% to 25% of patients with prediabetes (especially impaired glucose tolerance) also have neuropathy, and more than 25% of patients with neuropathy also have prediabetes.[6]

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The etiology of diabetic neuropathy is complex, but seems to relate to multifactorial microvascular damage.[5] Animal studies have revealed the involvement of many biochemical mechanisms.[7] Causative factors include hyperglycemia and subsequent metabolic changes, microvascular insufficiency, oxidative and nitrosative stress, defective neurotrophism, and autoimmune-mediated nerve destruction.[1,5] When patients have multiple contributing pathogenic factors, the exact etiology is difficult to discern.

It is known that the hyperglycemia associated with diabetes and prediabetes tends to reduce nerve perfusion, which then impairs the ability of the nerves to undergo repair and regeneration. Experimental studies suggest that oxidative and nitrosative stress contribute to deficits in nerve perfusion and conduction, dysfunction of small sensory nerve fibers, and morphological manifestations of peripheral neuropathy.[7] Additional metabolic changes associated with chronic hyperglycemia include increased polyol flux, accumulation of advanced glycation end products, and lipid abnormalities.[2]

## Signs and Symptoms

A frequent misconception is that diabetic neuropathy is a single condition, whereas it actually describes a heterogeneous group of disorders with a wide range of presenting symptoms.[3] The range of clinical syndromes may affect either the somatic or autonomic nervous system, or both.[1,3] The neuropathies may be focal or diffuse, proximal or distal.[1] Any organ of the body may be affected, from the gastrointestinal system to the skin, leading to a vast array of manifestations.[8]

Distal symmetric polyneuropathy is the most widely recognized form of diabetic neuropathy. It may affect either sensory or motor symptoms, and may involve small fibers, large fibers, or both.[3] Distal symmetric polyneuropathy is thought to result from nerve and blood vessel changes due to prolonged hyperglycemia, and can occur in either type 1 or type 2 diabetics.[5]

Small fiber neuropathies may be some of the earliest to develop, often presenting without objective signs or electrophysiologic evidence, but with symptoms of superficial pain (burning, tingling, allodynia). As the condition progresses, there is numbness and a loss of thermal perception, but reflexes and strength remain normal.[3] These somatic symptoms (tingling, numbness, pain) typically have a symmetric glove-and-stocking distribution, starting in both feet and spreading upwards, reaching the hands in severe cases.[1,5]

Large fiber nerve dysfunction manifests as loss of vibration, touch, and position sensation, along with impairment of motor coordination.[1,3] Objective physical features of large fiber neuropathy include a reduction in ankle and knee reflexes, loss of proprioception and resulting incoordination, and mild muscle weakness. Severe weakness is rare, and its presence may indicate other types of neuromuscular pathology.[1]

Some patients also describe spontaneous pain that coexists with loss of sensory function.[7] There are several varieties of pain associated with diabetic neuropathy, but most patients with pain report that it is worse at night, which tends to lead to sleep disturbances and sleep deprivation.[3,9] The experience of significant pain during the day, combined with lack of sleep at night, leads to great distress and is often the primary reason that patients with diabetic peripheral neuropathy seek medical attention.[9]

Although neuropathic pain may resolve spontaneously, pain that persists for more than 3 months is unlikely to do so, and can cause significant sleep disruptions, depression/anxiety, and impairment of quality of life.[3] Overall, approximately 10% of patients with diabetes experience persistent pain from neuropathy.[3] Small-fiber symptoms generally have a greater effect on quality of life, whereas large-fiber symptoms are more likely to interfere with coordination and other activities of daily living.[3]

Diabetic peripheral neuropathy is also frequently accompanied by diabetic autonomic neuropathy, although this is among the least recognized and understood complications of diabetes.[1,10] When the autonomic nervous system is affected, damage may be caused to the cardiovascular, gastrointestinal, and genitourinary systems, leading to symptoms such as tachycardia, sweating, sexual dysfunction, and difficulties with urination and bowel function.[4,8] Metabolic functions such as glucose counterregulation may also become impaired, making it more difficult for patients to feel when they are becoming hypoglycemic.[8]

Of all the complications of autonomic neuropathy, the most dangerous is cardiac autonomic neuropathy, which causes damage to the autonomic nerve fibers in the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics. Cardiac autonomic neuropathy is a significant cause of morbidity and mortality, and is associated with a high risk of cardiac arrhythmias and sudden death, possibly related to silent myocardial ischemia.[10]

## Disease Progression

Diabetic neuropathies tend to develop slowly over the years, either progressing undetected or presenting with nonspecific symptoms that mimic those seen in other diseases, requiring diagnosis by exclusion.[3] Over time, the frequency of neurologic complications generally increases with the duration of diabetes.[4]

The development of vascular complications may begin with an underlying genetic predisposition. The presence of

diabetic risk factors, such as dyslipidemia, hypertension, obesity, or smoking, can initiate inflammatory changes including oxidative and nitrosative stress. The combination of an inflammatory cascade and elevated blood glucose eventually leads to endothelial dysfunction and vascular complications.[3] From the time of the development of hyperglycemia, there is a much greater risk of developing neuropathy.[4] Once neuropathy has developed, its progression is closely related to the level of glycemic control in both type 1 and type 2 diabetes.[3]

When neuropathy begins to disrupt nerve pathways in the legs that are responsible for posture and gait, patients are more likely to experience falls during standing or walking.[11] Patients with "stocking and glove" neuropathy often lose touch sensation and proprioception, increasing the risk for imbalance and falls.[11] As patients get older, this becomes even more of an issue. Older patients without neuropathy already have a 30% fall risk, but older patients with neuropathy have approximately double the risk, especially on irregular surfaces and in low light conditions.[12]

As neuropathy progresses, physicians should also remember to inspect their patients' feet regularly. If their shoes do not fit well, or they have deformities such as bunions that lead to increased pressure, they are at much greater risk for developing foot ulceration and subsequent gangrene and limb loss.[3]

## Shortcomings of Available Palliative Prescription Therapies

Because of the strong association between hyperglycemia and neuropathy, and because of the significant morbidity resulting from neuropathy, many studies have investigated whether improving glycemic control may counteract the pathogenesis of the neuropathy.[5] Indeed, there has been some evidence that tight glycemic control may prevent or slow the progression of diabetic neuropathy, but not reverse it, which is why additional treatments are still being investigated for use in conjunction with glycemic control.[5,13]

Studies suggest that other factors besides glycemic control, such as dyslipidemia and inflammation, are also involved in the pathogenesis of diabetic peripheral neuropathy.[13] The overall treatment plan should therefore include measures to reduce hyperglycemia and other macrovascular risk factors such as high blood pressure and lipid levels.[1] Additional recommended lifestyle modifications include exercise and weight reduction, smoking cessation, a diet rich in omega-3-fatty acids, and limitation of alcohol consumption.[1]

Two drugs (duloxetine and pregabalin) are approved in the United States for treatment of painful neuropathy, but they are only palliative and do not address the underlying pathology of the disease, nor do they improve sensation.[14] Many pharmacologic approaches have been used, including tricyclic antidepressants (eg, amitriptyline), serotonin and noradrenalin reuptake inhibitors (eg, duloxetine and venlafaxine), antiepileptic drugs (eg, pregabalin and gabapentin), opiates, and local treatments such as capsaicin.[9] These treatments have varying levels of efficacy, depending on the type of nerve fiber involved in the process producing the pain.[3] While some of these treatments give symptomatic relief, none of them actually changes the natural history of the disease.[9]

Selection of any of these treatments should take into account the potential contraindications, comorbidities, adverse effects, and cost. For example, tricyclic antidepressants are contraindicated in patients with a history of heart disease, in patients with orthostatic hypotension, and in elderly patients taking diuretics or antihypertensives. Also, duloxetine should not be prescribed in patients with liver disease, and the antiepileptic drugs should be avoided in patients with edema.[9]

Since treatment options remain limited, continuing research into other neuroprotective agents is ongoing.[5,14] Finding medications to effectively combat oxidative-nitrosative stress remains highly warranted.[7]

## The Role of Metanx® in Diabetic Neuropathy

Metanx® is a medical food dispensed by prescription for the clinical dietary management of endothelial dysfunction in patients with diabetic peripheral neuropathy.[15] It contains high concentrations of the bioavailable forms of folate (L-methylfolate calcium) 3 mg, vitamin B12 (methylcobalamin) 2 mg, and vitamin B6 (pyridoxal-5'-phosphate) 35 mg (LMF-MC-PLP [Metanx; Nestlé Health Science-Pamlab, Inc, Covington, LA]).[14]

The rationale for this preparation is that diabetic neuropathy may be worsened by nutrient deficiencies when blood flow to the nerves is restricted.[16] For example, vitamin B12 deficiencies are common in patients with diabetes, especially those using metformin, since metformin inhibits the absorption of cobalamin (the precursor to vitamin B12) and can triple the risk of developing neuropathy.[17] By providing bioavailable forms of 3 key nutrients, Metanx® may be able to help patients maintain blood flow to peripheral nerves and help facilitate nerve repair.[16] Specifically, Metanx® restores nitric oxide synthesis and reverses oxidative-nitrosative stress, which may lead to vasodilation and improved endothelial function; neutralizes superoxide and peroxynitrite, restoring normal glutathione levels; and prevents formation of advanced glycation end products, possibly via chelation of transition metals.[14,17]

Additionally, compared to the current US Food and Drug Administration (FDA)-approved pain therapies (pregabalin and duloxetine), Metanx® has relatively few contraindications or adverse effects. In a recent clinical study, adverse events were infrequent (with no single event occurring in more than 2% of patients) and mostly mild to moderate.[14]

## Conclusion

Diabetic neuropathy affects at least half of patients with diabetes, and has significant implications for morbidity, mortality, quality of life, and economic burden. It represents an ongoing management challenge for patients, caregivers, and physicians.

Only 2 pharmacologic treatments are FDA-approved in the United States for treatment of diabetic neuropathy, although many additional approaches have been used with varying success, but all of them provide only symptomatic relief without any effect on the underlying pathology.

With the advent of the medical food Metanx®, patients and prescribers have a new option. The ingredients in Metanx® have been shown to reduce the oxidative and nitrosative stress that leads to endothelial dysfunction.[7] In doing so, Metanx® has the potential to address the basic underlying pathogenesis of diabetic neuropathy, unlike the other drugs on the market.

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# A Randomized Trial of Metanx® in Patients with Type 2 Diabetes and Peripheral Neuropathy

There has been some anecdotal evidence that vitamins B6, B12, and folate may reduce symptoms of neuropathy in patients who have diabetes-related deficiencies of these vitamins. To investigate this hypothesis, Fonseca et al recently conducted a multicenter, randomized, double-blind, placebo-controlled trial, assessing whether Metanx® (a medical food containing these 3 vitamins) would improve objective measures of diabetic peripheral neuropathy.

The study population consisted of 214 patients (aged 25 to 80 years) with established type 2 diabetes and peripheral neuropathy characterized by abnormal sense of vibration (baseline vibration perception threshold [VPT] of 25-45 volts in either leg). Patients were randomly assigned to receive 24 weeks of treatment with either Metanx® or placebo.

Exclusion criteria included peripheral vascular disease; amputation or ulceration within 2 years before screening; Charcot neuroarthropathy; previous surgery to spine or lower extremity with residual pain or impaired mobility; severe arthritis causing pain upon walking; A1C >9% at screening; blood pressure >160/90 mm Hg or uncontrolled asthma or shortness of breath in the 2 months before screening; advanced renal disease (serum creatinine >2.5 times the upper limit of normal); pregnant or nursing; and history of alcohol or drug abuse within the past 3 years. Additionally, patients were not allowed to have had α-lipoic acid or B12 injection within 2 months before screening, and no more than 10 mg of B6 or 800 µg of folate within 2 months before screening. Patients needed to take the maximum dose of any anticonvulsant, but no current treatment with systemic steroids, immunosuppressives, or radiotherapy.

The primary endpoint was effect on VPT, as measured on the great toe of each foot. A key secondary end point was improvement in the Neuropathy Total Symptom Score (NTSS-6), which is a validated composite quantification of numbness, tingling, aching, burning or lancinating pain, and allodynia. The NTSS-6 was specifically chosen for this study because it measures sensation (2 items) as well as pain (4 items). Another secondary endpoint was the Short Form 36 (SF-36) Health Survey, which includes feelings of happiness, emotion, social function, and vitality. Plasma levels of folate, vitamins B6 and B12, methylmalonic acid (MMA), and homocysteine were also measured as secondary endpoints.

The results showed that vibration perception threshold did not change significantly, and therefore the primary endpoint was not met. However, patients receiving Metanx® consistently reported symptomatic relief, with clinically significant improvement in NTSS-6 scores at 16 weeks ($P$ = .013 vs placebo). This benefit was maintained through 24 weeks ($P$ = .033).

As expected, the measured plasma levels of folate and 5-methyltetrahydrofolate, vitamin B12, and pyridoxal-5'-phosphate (PLP) increased significantly, while MMA levels decreased. Homocysteine decreased by 2.7±3.0 mol/L with Metanx® versus an increase of 0.5±2.4 mol/L with placebo ($P$ = .0001). Improvement in NTSS-6 scores was related to baseline MMA and inversely related to baseline PLP ($P$ = .003) and metformin use ($P$ = .0215). Quality-of-life measures also improved, and the change was positively associated with MMA ($P$ = .007).

Adverse events were infrequent, with no single event occurring in ≥2% of subjects.

In conclusion, this study provides evidence that Metanx® is a safe and effective therapy for alleviation of peripheral neuropathy symptoms, at least in the short term. Additional long-term studies should be conducted, as the trial duration may have been too short to show an effect on VPT. In addition, the authors suggested that further research on the effects in patients with cobalamin deficiency would be useful.

Based on Fonseca VA, Lavery LA, Thethi TK, et al. Metanx in type 2 diabetes with peripheral neuropathy: a randomized trial. *Am J Med.* 2013;126(2):141-149.

## Commentary by Vivian Fonseca, MD

The improvement in NTSS-6 scores appeared to be greatest in those patients who had high baseline levels of MMA (an indicator of vitamin B12 deficiency), low baseline levels of PLP (an indicator of vitamin B6 deficiency), and who were using metformin. This indicates that these patients had either spontaneous or metformin-related vitamin deficiencies, and that the Metanx® treatment helped relieve their symptoms through vitamin supplementation.

Overall our conclusion was that treatment with Metanx® was safe and effective to alleviate symptoms in people with diabetes and peripheral neuropathy, at least over the 4 to 6 month time frame. Additional long-term studies are needed to determine whether there is a significant effect on vibration sense. It may also be necessary to use other endpoints for assessment in future studies.

Further studies are needed to establish where Metanx® will fit in clinical practice. However, since the current FDA-approved treatments are only palliative and tend to have significant adverse effects, Metanx® provides a new option that appears to be relatively safe and effective.

# Efficacy of Metanx® in Treating Peripheral Neuropathy and Increasing Nerve Fiber Density in Zucker Diabetic Fatty Rats

The ingredients of Metanx® have been shown to counteract oxidative and nitrosative stress in vascular endothelium and peripheral nerve tissue, and to alleviate paresthesias and dyesthesias in patients with diabetic peripheral neuropathy (DPN). Shevalye and colleagues hypothesized that the combination product Metanx® might have even more efficacy against oxidative-nitrosative stress than its individual ingredients. With this in mind, the authors investigated the use of Metanx® to treat DPN in Zucker diabetic fatty (ZDF) rats, a model for type 2 diabetes.

At age 15 weeks, rats were weighed, blood samples for glucose measurements were taken from the tail vein, and assessment of motor and sensory nerve conduction velocities (MNCVs and SNCVs, respectively) and small sensory nerve fiber function was performed. Then, ZDF and ZDF lean rats were divided into groups maintained with or without Metanx® treatment for another 4 weeks, after which nerve functional studies were performed again.

An aqueous solution of Metanx® was administered at either 4.87 mg/kg/day (a body weight–based equivalent of human dose) or 24.35 mg/kg/day, by oral gavage 2 times a day for 4 weeks. Both doses improved sensory, but not motor, nerve condution in the hind legs. The treatment also alleviated thermal and mechanical hypoalgesia in the absence of any reduction of hyperglycemia. Low-dose Metanx® increased intraepidermal nerve fiber density, but did not prevent morphometric changes in distal nerve fibers.

The choice of ZDF rats as the animal subjects in this study was significant. Most animal studies of DPN have used rats with streptozotocin-induced type 1 diabetes, even though about 95% of Americans with diabetes have type 2. Very few reports describe DPN in animal models of type 2 diabetes. This study shows that the ZDF rat, which displays oxidative-nitrosative stress, MNCV and SNCV deficit, thermal and mechanical hypoalgesia, small sensory nerve fiber degeneration, and a mild atrophy of large myelinated fibers, is a robust animal model for studying the manifestations and treatment of DPN in type 2 diabetes.

The authors believe that Metanx® is the first oral therapeutic to show efficacy at alleviating both functional and morphological manifestations of experimental DPN at a body weight-based equivalent of human dose. The positive effect on intraepidermal nerve fiber density was also particularly striking, since a low-dose oral nutritional food would have advantage over the pharmacological approaches (recombinant human erythropoietin, insulin and insulin-like growth factor, or a glucagon-like peptide) tested in earlier animal studies.

Importantly, the efficacy of Metanx® was not due to reduction of diabetic hyperglycemia. It was likely due to the synergistic action of its components, counteracting oxidative and nitrosative stress; neutralizing superoxide and peroxynitrite; and the chelation of transition metals and preventing the formation of advanced glycation end-products.

The findings of this study provide new information on the manifestations and mechanisms of oxidative-nitrosative stress in experimental type 2 DPN. For example, the results suggest that the mechanisms of oxidative-nitrosative stress may be different in type 1 versus type 2 diabetes, and also different between large and small fiber neuropathies. The knowledge of these mechanisms, obtained from experimental studies, is important for selection of robust endpoints for clinical trials, many of which failed because of poor design and lack of sensitive measures of nerve function. Although it is always possible that clinical trial results may differ from animal study results, this experimental data suggests that Metanx® is more likely to have efficacy on small fiber neuropathies than large fiber neuropathies in human patients with diabetes.

The authors conclude by suggesting that their results, together with current knowledge of the mechanisms of oxidative and nitrosative stress in the pathogenesis of several diabetic complications, provide rationale for continued study of the effects of Metanx® on diabetic cardiovascular disease and retinopathy, as well as neuropathy.

Based on Shevalye H, Watcho P, Stavniichuk R, Dyukova E, Lupachyk S, Obrosova IG. Metanx alleviates multiple manifestations of peripheral neuropathy and increases intraepidermal nerve fiber density in Zucker diabetic fatty rats. *Diabetes*. 2012;61(8):2126-2133.

## Commentary by Aaron Vinik, MD, PhD

In the animal model, oxidative and nitrosative stress is associated with an impairment of sensory nerve conduction velocity, a reduction in intraepidermal nerve fiber density, and an endpoint common in animal models called thermal or mechanical hyperalgesia.

The short term (4-week) treatment with Metanx® in this study showed a significant reduction in oxidative and nitrosative stress, as well as a reduction in advanced glycation end products, and an improvement in the small nerve fiber density in Zucker diabetic fatty rats. It is clear from these study results that Metanx® demonstrated improvements in sensory but not motor nerve conduction.

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