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Nutritional Approaches to Treat Diabetic Neuropathy: A Systematic Review

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Abstract Diabetic neuropathy of the lower and upper limbs is a debilitating condition occurring in as many as half of long-term diabetics. Many studies have reported that good blood glucose control can significantly reduce risk of heart disease and strokes in diabetics. However, other studies have also reported that good blood glucose control has at best a modest effect in treating peripheral neuropathy in type 2 diabetics. New approaches to treat peripheral neuropathy are clearly needed. Nutritional approaches offer great promise in treating and preventing diabetic neuropathy. Many human and animal studies have reported that nutritional supplementation with many nutrients can significantly reduce pain, significantly improve tactile sensitivity and significantly increase nerve conduction velocities in diabetic neuropathy patients. Such nutrients that have been reported to significantly improve peripheral neuropathy symptoms include α-lipoic acid, acetyl-l-carnitine, B-complex vitamins, vitamins D and E, omega-3 fatty acids, magnesium, zinc and herbs/ plant phytochemicals. Because many nutrients are often helpful to diabetic neuropathy patients, multifaceted nutritional approaches employing a broad range of nutrients may be more useful than supplementation with single nutrients.

Keywords Diabetes, Diabetic Neuropathy, α- Lipoic Acid, Carnitine, B-vitamins, Vitamin D, Omega 3 Fatty Acids

1. Introduction

Diabetes is a very common disease, with an estimated 20 million diabetics in the United States alone[1]. Diabetic neuropathy (also known as diabetic peripheral neuropathy) is also very common, occurring in an estimated 30 to 50% of all diabetics[1]. Diabetic neuropathy causes chronic pain and/or numbness in the feet and hands and sometimes the legs and arms, significantly slower peripheral nerve conduction velocities and is associated with significantly increased risk for diabetic foot ulcers and foot amputations[2]. Diabetic neuropathy is also associated with significantly slower walking speed and significantly more falls[3].

The 2 standard treatments for diabetic neuropathy include aggressive glycemic (blood glucose) control and medications to reduce pain[2,4]. Better glycemic control in type 2 diabetics has been associated with significantly lower rates of heart disease, stroke and peripheral vascular disease[2,5]. However, good glycemic control is generally associated with only modest improvements in diabetic neuropathy in type 2 diabetics, with greater glycemic control-related neuropathy improvements seen in type 1 diabetics[2,4]. A 2012 review of published studies on the effects of blood glucose control and diabetic neuropathy reported that better glycemic control was associated with significantly reduced neuropathy in 6 out of 7 studies involving type 1 diabetics but in only 3 of 8 studies involving type 2 diabetics[4]. By far the largest of these studies reported involved 10,251 type 2 diabetic patients with a hemoglobin A_{1C} of greater than 7.4% at the start[6]. This study reported that development of diabetic neuropathy symptoms were only slightly and non-significantly lower in patients receiving aggressive glycemic control (Hemoglobin A_{1C} goal of<6.5%) as compared to standard glycemic control patients (Hemoglobin A_{1C} goal of 7-8%)[6]. Many patients with excellent glycemic control still experience worsening diabetic neuropathy[2.4]. Clearly, additional treatments are needed to reverse or at least slow progression of diabetic neuropathy.

Much recent research has suggested that many nutrients may be helpful in preventing or partially reversing the effects of diabetic neuropathy. These nutrients include α-lipoic acid, acetyl-l-carnitine, omega 3 fats, B-complex vitamins, coenzyme Q_{10}, magnesium, zinc and phytochemicals from fruits, herbs and vegetables.

2. Methods

Papers used for this review were identified through a search of PubMed articles written in English. Many different keyword combinations were used including "diabetic neuropathy" or "peripheral neuropathy" and many different nutrients/ foods such as α-lipoic acid, acetyl-l-carnitine, omega 3 fats, B-complex vitamins, coenzyme Q_{10},

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magnesium, zinc and phytochemicals from fruits, herbs and vegetables. The listing of papers is not exhaustive, but papers were selected to represent many of the more recent and important studies. Care was taken to include studies which report both positive and null or negative outcomes. Most of the papers cited involve human studies, however, interesting studies with lab animals are reported if there is little or no published data on relationships between that nutrient and human diabetics. This review with focus on nutritional treatments and will not cover promising new topical treatments for diabetic neuropathy such as capsaicin.

3. Results

The following nutrients have shown at least some promise in treating peripheral neuropathy in various human and/or animal studies.

3.1. α-Lipoic Acid

The most studied nutrient used to treat diabetic neuropathy has been the fat-soluble antioxidant α-lipoic acid. A recent meta-analysis examined 15 studies of 1,058 diabetic neuropathy patients who were given 300 to 600 mg of α-lipoic acid or placebo[7]. Compared to the placebo patients, the patients treated with α-lipoic acid had significantly faster nerve conduction velocities (median and peroneal) and significant less subjective feelings of pain and weakness[7]. Few serious adverse side effects were reported from these studies (Han 2012). A 4-year study of diabetic neuropathy patients given either 600 mg α-lipoic acid (233 patients) or placebo (227 patients), reported that nerve conduction rates were not significantly different in either group but the α-lipoic acid treated group had significantly less symptoms of muscle weakness and neurological impairment[8].

3.2. Acetyl-l-Carnitine

Oral supplements of the amino acid l-carnitine or acetyl-l-carnitine may also be helpful to diabetic neuropathy patients. A large study of 1,257 patients in USA/ Canada/ Europe treated diabetic neuropathy patients with 1,500 or 3,000 mg acetyl-l-carnitine daily or placebo for one year. Compared to placebo, the patients taking 3,000 mg. acetyl-l-carnitine daily had significantly less pain in their extremites and had significantly better vibratory sensitivity in both their toes and fingers[9]. Improvements in pain and vibratory sensitivity were less in the group taking 1,500 mg acetyl-l-carnitine daily as compared to the 3,000 mg group. Patients from both the 1,500 and 3,000 mg, acetyl-l-carnitine groups showed significant increases in sural nerve fiber numbers as compared to placebo patients, suggesting that acetyl-l-carnitine may be helpful for nerve regeneration[9]. Another study reported that 1,500 or 3,000 mg of acetyl-l-carnitine daily significantly reduced the risk of diabetic neuropathy patients developing new-onset pain, with the protective effective being greater at patients receiving the 3,000 mg dose[10].

3.3. B-Complex Vitamins

Higher levels of the toxic metabolite homocysteine have been linked to significantly higher levels of diabetic neuropathy[11]. Various B-vitamins such as methylcobalamin (vitamin B_{12}), folate, and pyridoxal 5-phosphate (vitamin B_6) play a key role in lowering high levels of homocysteine in the blood. Vitamin B_{12} also plays a critical role in peripheral nerve repair and regeneration[12]. A study of 100 patients with type 2 diabetic neuropathy reported that 2,000 µg of intramuscular vitamin B_{12} twice weekly for 3 months produced significant drops in pain, drops than were significantly greater than a group of diabetic neuropathy patients treated with 10 mg of nortriptyline each night[13]. Studies with a diabetic neuropathy patients have reported that daily treatment with a supplement called Metanx® containing methylfolate (3 mg), and vitamins B_6 (35 mg)and B_{12} (2 mg) were associated with significant drops in pain and significant increases in lower extremity nerve fiber density[14-5]. A recent double-blind study treated 106 type 2 diabetic patients with Metanx® daily (containing methylfolate (3 mg), and vitamins B_6 (35 mg)and B_{12} (2 mg) and another 108 type 2 diabetic patients with placebo for 24 months[16]. Compared to the placebo patients, the patients treated with Metanx® had significant improvements in pain and other symptoms as well as significant improvements in quality of life scores. Mean homocysteine levels decreased by 2.7 µmol/L in the Metanex® treated group and increased by 0.5 µmol/L in the placebo treated group ($p=0.0001$). Few adverse side effects were reported in either the Metanx® or placebo groups. No significant improvements in vibratory perception threshold were seen in the Metanx® treated patients, although the authors suggested that the time period (24 weeks) may have been too short to see improvements and longer trials should be useful[16]

Metformin is a bigaunide drug that is commonly used to control blood glucose levels in diabetics. Several studies have reported that metformin use is associated with higher risk of vitamin B_{12} (cobalamin) deficiency[17]. An Alberta study reported that mean serum vitamin B_{12} levels were more than twice as high in 63 diabetics not treated with metformin (mean 486 pmol/L cobalamin) as compared to 59 diabetics treated with metformin for at least 6 months (mean 231 pmol/L, difference significant at $p<0.001$)[17]. Frank vitamin B_{12} deficiency (less than 210 pmol/L) was found in 18 of the metformin treated diabetics (31%) but in only 2(3%) of the non-metformin treated diabetics ($p<0.001$). Levels of serum homocysteine were significantly higher in the metformin treated diabetics versus the non-metformin treated diabetics (mean 11.6 µmol/L vs. µmol/L, $p<0.001$). In addition, clinical measures of peripheral neuropathy were significantly worse and nerve conduction velocities were significantly slower in the metformin treated diabetics as compared to the metformin treated diabetics. Since toxicity of vitamin B_{12} supplements are quite low, it seems prudent to

give all patients treated with metformin supplements of B_{12} or B-complex[17].

A number of other studies have used B-vitamin or B-vitamin combinations to treat diabetic neuropathy with at least some success. Significant improvements in pain severity and vibration perception thresholds were reported in a group of 30 diabetic neuropathy patients treated with 2 milligrams of Vitamin B_{12} and 400 milligrams of benfotiamine (a form of thiamine or vitamin B_1) daily for 9 weeks[18]. Another study of type 2 diabetic neuropathy patients treated 23 patients with mineral/ antioxidant vitamin supplements (zinc 20 mg., magnesium 250 mg, vitamin C 200 mg and vitamin E 100 mg daily), treated 22 patients with B-complex vitamins (B_1 10 mg, B_2 10 mg, B_6 10 mg, biotin 200 µg, B_{12} 10 µg and folate 1 mg daily) and treated 22 patients with placebo. Following 4 months of treatment, diabetic neuropathy symptoms were significantly reduced ($p=0.001$) in both the mineral/antioxidant vitamin supplement group and the B-vitamin supplement group as compared to placebo[19]. A meta-analysis of 7 published studies reported that supplementation with vitamin B_{12} or vitamin B complex mixtures containing B_{12} significantly improved pain and paresthesia in diabetic neuropathy patients[20]. The effects of B_{12} or B-complex supplementation were not consistent in terms of changes in nerve conduction velocities or vibration sensitivities[20]. A case series was presented of 3 patients with severe peripheral neuropathy who improved dramatically following treatment with 5 milligrams of biotin for 1 to 2 years[21]. All of the B-vitamins probably play an important role in nerve health, and it seems prudent to treat diabetic neuropathy patients with fairly high doses of all of the B-vitamins.

3.4. Vitamins D and E

Vitamin D deficiency is very common in diabetics, with one study of 62 diabetic neuropathy patients reporting that 59 (95%) were seriously deficient in vitamin D (25[OH]D<20 ng/ml serum)[22]. A US study of 591 diabetic adults over age 40 reported that low or borderline low Vitamin D levels (25[OH]D<30 ng/ml) were associated with a significantly higher risk of peripheral numbness (OR 2.04, 95% CI 1.18-3.52)[23]. A recent case study reported on a type 1 diabetic with low vitamin D levels whose peripheral neuropathy symptoms abated dramatically in just 4 weeks with treatment of 50,000 international units of vitamin D weekly[24]. Studies of vitamin D supplementation in diabetic neuropathy patients are badly needed[22].

A small study of 21 type 2 diabetics reported that patients who received 900 milligrams of vitamin E daily for 6 months had significantly higher median nerve conduction velocity as compared to patients given placebo. Glycemic control was not significantly different among the vitamin E and placebo treated patients[25].

3.5. Essential Fatty Acids

Other nutrients may play a role in preventing and treating diabetic neuropathy. A Japanese study of 21 type 2 diabetic neuropathy patients reported that daily supplementation of purified fish oil containing 1,800 mg of EPA (eicospentaenoic acid- an omega 3 fatty acid) for 48 weeks was associated with significant improvements in numbness and vibratory thresholds in the feet, as well as decreased amounts of albumin in urine[26]. Another study of 22 diabetic neuropathy patients reported that daily supplementation with 360 mg of gamma-linolenic acid (an omega-6 fat from evening primrose oil) for 6 months was associated with significantly better neuropathy symptoms and peripheral nerve velocity as compared to diabetic neuropathy patients given placebo[27].

3.6. Minerals

Magnesium levels are often low in diabetics. A study of 110 magnesium depleted type 1 diabetic patients reported that that 300 mg daily magnesium supplementation for 5 years was associated with less risk of polyneuropathy as compared to patients given placebo[28]. Another study reported significant improvement of peripheral nerve conduction velocities in 60 diabetic neuropathy patients treated with 267 mg of zinc daily[29].

3.7. Herbs

Use of herb mixtures are commonly used in Chinese herbal medicine to treat diabetic neuropathy. A meta-analysis of 18 Chinese studies treated diabetic neuropathy patients with either herbal mixtures or vitamin B_{12} and/or B_1 as a control[30]. Herbs used to treat diabetic neuropathy patients included Astragalus Radix (huangqi) (13 studies), Angelicae Sinesis Radix (danggui) (12 studies), Pheretime (dilong) (10 studies) and 10 other herbs. Meta-analysis of these studies reported that subjective diabetic neuropathy symptoms, tendon reflex and nerve conduction velocity improved in the patients given mixtures of Chinese herbs as compared to vitamin B_{12} and/or B_1 as a control. However, none of these 18 studies were double-blinded, none reported possible adverse effects, and many of these 18 studies were of poor methodological quality. The authors recommended more rigorous study of Chinese herbal treatment on diabetic neuropathy patients[30].

3.8. Nutritional Studies with Animal Diabetic Neuropathy

In a rat type 2 diabetic model, supplementation with coenzyme Q_{10} was reported to prevent peripheral neuropathy and attenuate neuron loss[31]. Another study with diabetic rats reported that high dose oral n-acetyl cysteine (1.5 gr/ Kg weight/ day) was able to significantly inhibit oxidative stress and peripheral neuropathy[32]. Several studies with diabetic lab rats have reported that diets supplemented with the amino acid taurine is associated with significantly better peripheral nerve velocity, significantly better nerve peripheral blood flow and significantly better sensory thresholds as compared

to rats not provided with taurine[33-4].

Phytochemicals from vegetables and fruits may also be helpful in treating peripheral neuropathy. A rat diabetic study reported that grape seed proanthocyanidin extracts improved peripheral nerve function[35]. A mouse diabetic study reported that lycopene (found in tomatoes and watermelon) attenuated heat related pain[36]. Feeding cinanamon (*Cinnamomum cassia* 400 mg/ Kg with rat chow) to diabetic rats significantly reduced peripheral neuropathy as compared to rats fed only rat chow[37]. Other studies with diabetic rats have reported that supplementation with resveratrol (from grapes) and sulforaphane (from broccoli and other cruciferous vegetables) are associated with significantly less severe diabetic neuropathy[38-9].

4. Discussion

Many nutrients are needed to maintain proper health of nerves and blood vessels in diabetics. In addition to proper glycemic control, diabetics require a well balanced diet and a broad spectrum of food supplements including α-lipoic acid, acetyl-l-carnitine, B-complex vitamins, vitamin D, and essential fatty acids. Animal studies have also suggested that phytochemicals from fruits, vegetables and herbs may also play an important role in preventing and treating diabetic neuropathy and other diabetic complications. Much more human study is needed to examine the possible beneficial effects of phytochemicals on diabetic patients [40].

Many of the reports cited in this review study the effects of supplementing with a single nutrient on diabetic neuropathy. Since so many nutrients are potentially helpful for preventing and treating diabetic neuropathy and other diabetic complications, experimental studies utilizing only one nutrient or food may not produce statistically significant improvement [41]. Therefore, future studies on diabetic neuropathy should concentrate on using numerous nutrients simultaneously in a "bundled" fashion. Much more clinical and research attention is needed to develop optimum nutritional strategies to prevent and treat diabetic neuropathy.

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