Diagnosis and Treatment of Painful Diabetic Peripheral Neuropathy

Pop-Busui R, Ang L, Boulton A JM, Feldmann EL, Marcus RL, Mizokami-Stout K, Singleton JR, Ziegler D
Arlington (VA): American Diabetes Association; 2022 Feb.

At a glance:

- The American Diabetes Association's Clinical Compendium provides a comprehensive overview on the epidemiology, pathophysiology, screening, diagnosis and treatment of diabetic peripheral neuropathy (DPN). In addition, the therapeutic role of "nutraceuticals" is explained in detail, which is summarized in the following. (Scan the QR Code below for access to the original full publication)
- The limited efficacy of causal therapies for DPN results in a need for pathogenetically oriented adjunctive treatment using nutraceuticals.
- The use of α-lipoic acid (ALA) and benfotiamine in DPN therapy is supported by their efficacy demonstrated in randomized controlled trials (RCTs) in reducing DPN symptoms, including pain, as well as their excellent safety profile.

Introduction & Background

The most common complication in patients with diabetes is diabetic neuropathy, with a lifetime prevalence of over 50%. Among various forms of diabetic neuropathies, DPN is the most common and therefore the most important clinical manifestation. It is predictive for the development of neuropathic foot ulcers, overall mortality and cardiovascular morbidity. Despite its importance, the disease remains underdiagnosed and lacks effective causal treatments.

Role of Nutraceuticals in DPN

"Nutraceuticals" include biofactors and intent not only to supplement the diet but also to help prevent or treat diseases. Numerous biofactors are essential for the normal physiological functions of the body and exert health-promoting or disease-preventing biological activities. Essential biofactors, such as vitamins and minerals, cannot or not sufficiently be synthesized by the body itself and must be provided by external sources. Since diabetes is associated with systemic deficiencies of several biofactors and beneficial effects have been reported in the absence of these deficiencies, dietary supplementation with certain biofactors could provide a benefit in addition to established DPN therapy. In contrast to standard analgesic therapy, which can only symptomatically alleviate neuropathic pain, the aim of treatments based on nutraceuticals is primarily to positively influence the underlying neuropathic process and the related clinical consequences.

Among nutraceuticals, the best evidence in the treatment of DPN is available for the use of ALA. Treatment with the antioxidant ALA aims to reduce oxidative stress, which plays an important role in the underlying pathomechanisms of DPN. Previous studies showed that ALA administered intravenously (600 mg/day for 3 weeks) improves neuropathic symptoms and deficits. Regarding oral use, it was shown that 5 weeks and 6 months of treatment with ALA (600 mg/day and 2x daily, respectively) could reduce the main symptoms of DPN, including pain, paresthesias and feeling of numbness. The NATHAN 1 study included patients with diabetes and DPN (n = 460) and showed an improvement in neuropathic deficits after four years of oral ALA treatment (600 mg/day), suggesting a positive impact on the underlying neuropathy. Overall, the drug was well tolerated throughout the complete study period and further clinical and monitoring studies also point to a favorable safety profile of ALA. Based on the results of the NATHAN-1 trial, ALA (600 mg daily) may be considered for long-term use (≥4 years) in asymptomatic DPN. If symptoms are only partially relieved (≤30 %), the authors state that it may occasionally be helpful to increase the usual dosage of 600 mg ALA daily to 600 mg twice or three times daily.

Vitamin B1 serves as a cofactor for enzymes of the carbohydrate metabolism and the precursor benfotiamine can inhibit the formation of advanced glycation endproducts. A reduction in neuropathic symptoms through a 6-week treatment with benfotiamine (300 mg/2x daily) was shown in the BENDIP study. The BEDIP study showed that three weeks of benfotiamine treatment (400 mg/day) improved neuropathic symptoms and signs, without difference in adverse events between the treatment and placebo groups. Whether a dose of 600 mg per day should be maintained during long-term treatment is currently being investigated in the BOND study, where 300 mg benfotiamine twice daily is used.

Patients treated with metformin are at higher risk of vitamin B12 deficiency. In addition to hematological consequences, vitamin B12 deficiency can also have neurological manifestations, including polyneuropathies. A 12-month RCT evaluating the effects of oral vitamin B12 supplementation (1,000 µg/day) in type 2 diabetic patients receiving metformin and with low vitamin B12 levels (<400 pmol/L) and neuropathy found improvements in neurophysiological measures, pain score, sudomotor function and quality of life with B12 supplementation. While vitamin B12 deficiency should be treated with 1,000 µg of oral vitamin B12 daily, treatment of DPN with vitamin B12 without proven B12 deficiency is not indicated.

A study of type 2 diabetes patients with DPN, mostly vitamin D deficient, observed improvements in neuropathic symptoms and deficits after 24 weeks of high-dose vitamin D treatment (40,000 IU/week) compared to the control group receiving 5,000 IU/week vitamin D. However, further studies investigating this association are needed. As severe vitamin D deficiency <30 nmol/L (<12 ng/ml) increases mortality due to infections and other diseases, it should be avoided in any case.

Magnesium is involved as cofactor in many reactions of carbohydrate metabolism. Both low magnesium levels and low magnesium intake have been associated with prediabetes and diabetes. However, there are no RCTs demonstrating the efficacy of magnesium supplementation in DPN. For patients with diabetes and hypomagnesaemia, magnesium supplementation is recommended when dietary measures fail to balance magnesium status. Oral magnesium supplementation of up to 350 mg/day can be considered safe.

Summary & Conclusion

The efficacy and safety of various nutraceuticals, including ALA, benfotiamine, vitamin B12 and vitamin D, have been studied in RCTs. ALA and benfotiamine are already approved as pharmaceuticals for the treatment of DPN in several countries and their use is recommended in guidelines. Especially the efficacy of ALA was highlighted in several meta-analyses. Patients deficient in vitamin B1 and vitamin D or magnesium should receive supplementation to prevent DPN and other disorders from worsening. The advantage of nutraceuticals is their excellent safety profile. Overall, nutraceuticals have the potential to positively influence the course of DPN and ultimately contribute to the expansion of the therapeutic armamentarium regarding this complication of diabetes.

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