EDITORIAL

Role of Vitamins in Advanced Therapy for Parkinson's Disease: Decoding the Paradox

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The relationship between vitamins and Parkinson's disease (PD) has been explored in many clinical studies, animal models, and single-cell experiments. In PD, vitamins act as cofactors in enzymatic pathways of dopamine metabolism, affect pharmacokinetics of levodopa, and play neuroprotective roles by mitigating neuroinflammation and oxidative stress.

A critical role of central and peripheral inflammation has been emphasized in the recent literature regarding the onset and progression of PD.[1–3] Supplementation of vitamins with known anti-inflammatory, antioxidant, and free radicle scavenging properties is thus one of the major neuroprotective strategies under recent focus in PD.[4,5] A recent Swedish trial has demonstrated an inverse correlation between dietary vitamins E and C intake and the risk of PD, especially in overweight and obese patients.[6] Vitamin C can enhance levodopa absorption that can help to manage 'delayed on' or 'poor on' response in PD patients. Ascorbic acid also plays a major role in the biosynthesis of norepinephrine in sympathetic neurons and thus is a potential therapeutic target for managing orthostatic hypotension in PD.[7] Some studies have shown a correlation of vitamin D receptor polymorphism with risk of PD, though the results are inconsistent.[8] Similarly, two prospective trials have shown contradictory results on the relationship between mid-life serum vitamin D levels and the risk of PD.[9,10] Vitamin D supplementation has also been noted to improve balance and decrease fall risk in PD patients. However, the dose- and time-dependent effects of these vitamins need to be evaluated further.[11,12]

Apart from vitamins E, C, and D, vitamin B complex also has a major impact in PD management. In the current issue of the Journal, Taher et al. have highlighted the physiology and pathophysiology of vitamins B_6 (pyridoxine), B_9 (folate), and B_{12} (cobalamin) in PD patients undergoing levodopa–carbidopa intestinal gel (LCIG) therapy.[13] An anonymous survey conducted in February 2020 among neurologists, gastroenterologists, and clinical nurses from across Canada has served as a prelude to the manuscript. The survey clearly revealed the knowledge gap and inconsistencies among individual practices on multiple facets in this regard. Thus, the unmet need of a therapeutic recommendation had to be addressed.

Peripheral neuropathy is a well-known complication of chronic levodopa therapy. Studies have shown that cumulative doses of levodopa, deficiencies of vitamins B_6, B_9, B_{12}, and genetic factors play major roles in causing neuropathy and result in elevation of methylmalonic acid (MMA) and homocysteine. Neuropathic complications can be acute like Guillain–Barré syndrome, subacute, and chronic.[14] Patients receiving levodopa daily dose (LDD) of beyond 2,000 mg and in whom LDD is rapidly increased within a short interval, like during the initiation of LCIG therapy, are at high risk of developing this side effect.[15] High homocysteine and low pyridoxine are the major culprits on this regard. Two pathophysiological mechanisms have been highlighted: (1) Co-administration of levodopa and dopa decarboxylase inhibitor (carbidopa) increases levodopa metabolism by catechol-O-methyltransferase (COMT) that converts it to 3-O-methyldopa. For this conversion, COMT requires S-adenosylmethionine (SAM) as the methyl-group donor and that in turn facilitates conversion of SAM into S-adenosylhomocysteine and subsequently increased homocysteine production. Homocysteine can enter either into the transmethylation cycle and convert into methionine by methionine synthase (vitamin B_{12} and folate as cofactors) or into transsulfuration pathway and converts into cystathionine by cystathionine beta-synthase (vitamin B_6 as co-factor). In case of deficiency of these vitamins, neurotoxic effects of hyperhomocysteinemia manifest; and (2) Carbidopa irreversibly binds to pyridoxal phosphate (PLP, active form of vitamin B_6) and permanently deactivates PLP-dependent enzymes like many decarboxylases and depletes pyridoxine reserve pool.[13] While vitamin B_6 deficiency can cause small fiber neuropathy, epilepsy, and encephalopathy, vitamin B_{12} deficiency can lead to large fiber neuropathy or dorsal column involvement. Autonomic neuropathy involving visceral nerves can cause gastroparesis that can lead to constipation and insufficient absorption of levodopa and dietary vitamins, further enhancing the vicious cycle.

The authors have also discussed two potential mechanisms explaining why the risk of vitamin deficiencies and peripheral neuropathy is more common during LCIG therapy in comparison to oral levodopa: (i) methylcellulose gel used in LCIG may hinder absorption of the dietary vitamins through jejunal membrane; and (ii) continuous delivery of LCIG may saturate the one-carbon pathway being used in levodopa metabolism because of the absence of 'metabolic rest' needed to utilize those vitamins for other metabolic functions.[13]

Finally, the paper has nicely summarized a therapeutic guideline on testing and managing vitamin deficiencies in PD patients undergoing LCIG therapy. Vitamin B_{12}, homocysteine, and MMA must be tested before starting LCIG, after 6 months, and then once a year. Nuances of these tests should be kept in mind

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while ordering them to avoid misinterpretation of laboratory test results. Vitamin B_6 and/or folate should be measured in scenarios of raised homocysteine with normal MMA and/or total vitamin B_{12}. Plasma PLP, serum/red blood cell folate, and total B_{12} and/or MMA are recommended tests for vitamin B_6, B_9, and B_{12}. Nerve conduction study should be done before starting LCIG to look for any pre-existing neuropathy and once a year subsequently to monitor the development or progression of neuropathy. Prophylactic vitamin B_{12} and vitamin B_6 supplementation is needed for high-risk individuals. However, clinicians must be aware of the neurotoxic side effects of excess vitamin B_6 and potential risk of inducing neuropathy with folate supplementation in patients with vitamin B_{12} deficiency. COMT inhibitors can be added to manage hyperhomocysteinemia. Therapeutic dose of cyanocobalamin, folic acid, and pyridoxine is needed to manage vitamin deficiencies and resulting side effects like peripheral neuropathy. In advanced cases, temporary discontinuation of LCIG therapy may be needed along with supportive therapeutic alternatives like subcutaneous apomorphine.

Clinicians are using advanced therapeutic options like LCIG to manage motor fluctuation more efficiently and to offer a better quality of life in PD patients. However, the complex pharmacology and biochemistry underneath it should be understood clearly to avoid potential side effects. Adequate knowledge of monitoring and treating those side effects is also important. Having said that, the clear dose–response relationship between the vitamins and their therapeutic effect has not been established. Especially in scenarios like PD, where brain biochemistry and body physiology are already altered, fine-tuning the supply of micronutrients to match with the changing metabolic demands is much harder than it seems. Further prospective studies are needed to address these issues.

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Statement of Authorship

JG and MTB wrote the first draft of the manuscript; critically reviewed by MJ.

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