

Understanding the Role Diet Plays in Parkinson's Disease Could Lead to Better Disease Management

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Parkinson's disease (PD) is a progressive and incurable neurodegenerative disease of the central nervous system that usually develops in individuals after the age of 50. PD is characterized by motor symptoms, including shaking, rigidity, slowness of movement and gait impairment, that are caused by the loss of dopaminergic neurons in substantia nigra pars compacta (SNpc) of the midbrain. Additional symptoms of the disease include autonomic dysfunction (i.e. gastrointestinal, urinary, sexual, orthostatic hypotension and excessive sweating), sleep problems, sensory problems and neuropsychiatric problems (i.e. depression, anxiety, dementia and psychosis) [1].

Most cases of PD are sporadic with an unknown etiology. Currently it is thought that environmental factors and genetic susceptibility are both important in disease development [2]. PD is characterized by mitochondrial dysfunction, inflammation, dysfunction of the autosome-lysosomal autophagy system [3] and endoplasmic reticulum stress [4]. The pathological manifestation of the disease is characterized by accumulation of alpha synuclein inclusions in neurons referred to as Lewy bodies [5].

Currently there is no cure for PD. Motor symptoms of the disease are most often treated using levodopa and dopamine agonists. As the disease progresses, more neurons are lost, the drugs become less effective and some patients develop disabling dyskinesias. In addition, several studies indicate an increasing risk of malnutrition among PD patients and that malnourished patients remain under-recognized by health professionals [6,7]. In fact, a recent study revealed that approximately 30% of patients with mild to moderate PD are at risk of malnutrition [7]. This finding suggests that PD patients with more severe symptoms may be at even higher risk of malnutrition.

Neuronal cell growth and development requires a wide range of nutrients including protein, iron, zinc, selenium iodine folate, vitamin A, and long-chain polyunsaturated fatty acids [8]. A balance of these nutrients is necessary for both the developing and aging brain. The brain is vulnerable to nutritional insults as we age, which can sometimes lead to irreversible damage. For example, diets that are high in saturated fats are implicated in cognitive dysfunction and increased risk for neurological disease, whereas diets rich in omega 3 fatty acids may reverse these detrimental effects [9]. More broadly, the relationship between the brain and nutrition can be exemplified with the increased risk in neurological disease among patients suffering conditions associated with the metabolic syndrome. Specifically, patients with diabetes mellitus often develop neurodegenerative diseases such as PD and Alzheimer's disease (AD) [10-12]. Increasing evidence suggest that impaired insulin signaling and other common dysregulated processes lead to neurodegeneration.

Our understanding of the impact of nutrients in PD patients is in its infancy. Evidence from experimental and clinical medicine suggests that some nutrients may exert neuroprotective effects, whereas other dietary constituents may be detrimental for PD patients [13]. The impact of nutrients has been implicated in the biological pathways that mediate neurodegeneration including mitochondrial dysfunction, inflammation, and oxidative stress as well as in novel mechanisms that promote neuroprotection.

Nutritional constituents associated with a possible decreased risk of PD include phytochemicals present in fruits and vegetables. Fruits and vegetables rich in antioxidants including vitamin A, B and C, and carotenoids may benefit PD patients and reduced disease risk [14,15] reviewed in [13]. Vitamin D supplementation appears to be neuroprotective in models of PD [16,17]. These studies are partly based on the observation that vitamin D3 deficiency is highly prevalent among PD patients [18,19]. A phase 2 clinical trial is currently testing the effects of vitamin D3 on balance, gait, falls, strength and cognitive performance in PD patients (NCT01119131). Another ongoing clinical trial of vitamin D in PD is designed to determine whether vitamin D improves motor and cognitive functions of patients with PD (NCT00571285).

In addition, evidence from *in vitro* and animal models possibly indicate that omega-3 polyunsaturated fatty acids (PUFA) exert neuroprotective effects in PD [20,21]. Although the evidence from clinical trials is very limited, one study showed that supplementation with omega-3 PUFA reduced depression in PD patients [22]. Like depression, dyskinesias resulting from symptomatic treatments such as levodopa also have a great impact in the quality of life of PD patients [23]. A phase 1 clinical trial for PD is designed to evaluate omega-3 fatty acids for the treatment of levodopa induced dyskinesia (LID) in PD patients (NCT01563913).

Caffeine is perhaps the most widely studied neuroprotective agent in PD. Several lines of research strongly indicate that caffeine reduces dopaminergic toxicity through antagonism of adenosine A_{2A} receptors [24,25]. Increasing experimental and epidemiological evidence indicates that caffeine elicits neuroprotection and improves motor and non-motor symptoms in PD patients [26-28]. In this regard, an upcoming clinical trial will evaluate the efficacy of caffeine intake on the motor and non-motor aspects of PD (NCT01738718). In addition other compounds found in coffee including eicosanoly-5-hydroxytryptamide have shown promise as neuroprotective agents in animal studies and warrant further studies in humans.

In contrast, consumption of dairy products and milk appear to possibly increase risk of PD [29,30]. The detrimental effects may be explained by the presence of potential toxins in some dairy products. However, the specific component of milk or the underlying mechanism has not yet been determined. Thus, more rigorous studies including

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organic dairy products are needed to assess the impact of dairy products and its constituents in neurodegeneration.

In addition to studies on individual nutrients, we also need more studies to determine whether specific diets may be beneficial for PD patients. Although the epidemiological evidence regarding the neuroprotective effects of fruits and vegetable is conflicting [15] recent studies suggest it may reduce risk of PD [14,31]. A current clinical trial is comparing the impact of a healthy high carbohydrate (50% of daily calories) diet including fruits and vegetables to a low carbohydrate diet (≤ 20 g per day) in PD (NCT00777010). Previously, a small feasibility study found that a ketogenic diet consisting of high fat and very low carbohydrate intake improved motor symptoms in PD patients [32] suggesting that this should also be tested in a clinical trial. Another promising diet for neurodegenerative diseases is the Mediterranean diet, characterized by the high intake of vegetables, legumes, fruits, grains, monounsaturated fatty acids, fish, low to moderate consumption of dairy products, meat and poultry and moderate consumption of red wine. Higher adherence to a Mediterranean diet has been associated with a reduced risk of cognitive decline and essential tremor [33,34], conditions associated with neurodegeneration. Furthermore, adherence to a Mediterranean diet may be associated with a reduced risk of PD, whereas low adherence is associated with an earlier age of onset [35].

In conclusion, our current state of knowledge about the role nutrients and diet play in PD is very limited. Because of these limitations physicians usually limit their dietary recommendations for patients to eat a well-balanced diet that includes increased fiber intake to prevent constipation. In addition, they may make medication-specific suggestions such as moderation in eating air-dried and fermented foods if the patient is taking a MAO-B inhibitor. Ideally, however, we would like to have a better understanding of how specific nutrients and diets influence the course of PD so that clinicians may provide more extensive recommendations. What we need are large randomized longitudinal clinical trials in order to establish which nutrients or diets are beneficial for PD patients. Ideally, these studies will take an integrative approach to analyze the data including genomics, transcriptomics and network analysis [36]. Incorporation of patients at risk for PD and individuals with a genetic predisposition to the disease in the trials will be crucial to identifying nutrients or diets that may slow the progress of the disease.

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