Preventing and Treating of Parkinson's Disease with a Plant-Based Diet

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Submission: March 22, 2021; **Published:** April 28, 2021

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Abstract

Parkinson's Disease (PD) is the second most common human neurodegenerative disorder, but no current therapy has been proven to be disease-modifying. Epidemiological as well as interventional studies indicate that the plant-based diet has the potential to prevent and treat PD. There are pathophysiological reasons that make this likely to be true. The Western diet is among the greatest risk factors for developing neurodegenerative diseases such as PD. Consumption of high quantities of animal saturated fat has been widely reported to be associated with increased risk of developing Parkinson's disease. Pesticide, herbicide, and heavy metal exposures through the consumption of meat are linked to an increased risk of Parkinson disease in some epidemiologic studies. Interventional studies with a plant-based diet have achieved positive results.

Accumulating evidence indicates that oxidative damage and mitochondrial dysfunction contribute to the cascade of events leading to degeneration of dopaminergic neurons. In addition, dysbiosis of the gut microbiota may be involved in the pathogenesis of PD, inducing immune cell activation and neuroinflammation of the central nervous system. The benefits of a plant-based diet result from the increased levels of phytonutrients and the intake of fiber, which supports a beneficial gut microbiota and decreases the incidence of constipation, an independent risk factor. A plant-based diet can also facilitate the use of a protein-redistribution diet to improve the effectiveness of treatment with L-dopa.

Keywords: Dopaminergic; Gut dysbiosis; Inflammation; Microbiota; Neurodegenerative; Oxidative stress; Parkinson's; Pesticide; Plant-based diet; Protein-redistribution

Abbreviations: 6-OHDA – 6-hydroxydopamine, CNS - central nervous system, CSF - cerebrospinal fluid, FA – Ferulic acid, nAChR - nicotinic acetylcholine receptors, PD – Parkinson's Disease, RBD – rapid eye movement sleep behavior disorder, ROS - reactive oxygen species, SCFA - short chain fatty acids, SNpc - substantia nigra pars compacta, UPDRS - unified Parkinson's disease rating stage.

Introduction

With aging and increasing life span of the global population, age-related diseases like Parkinson's Disease (PD) are receiving increased attention from the scientific community. Neurological disorders are now the leading source of disability in the world, and PD is the fastest growing of these disorders [1]. It is, after Alzheimer's disease, the second most common human neurodegenerative disorder. The total annual cost of Parkinson's Disease in the United States is almost $52 billion [2]. The main signs of PD include bradykinesia, which is the cardinal symptom, plus muscular rigidity, rest tremor, and gait impairment. The characteristic pathological finding associated with the motor signs of PD is degeneration of the dopaminergic neurons of the pars compacta of the substantia nigra, resulting in loss of dopamine in the striatum [3]. It is now thought that the involvement of non-dopaminergic pathways in the evolution of PD account for the increasingly recognized non-motor symptoms that adversely impact the quality of life of patients with PD [4,5,6].

The prodromal phase (up to 15–20 years before onset of motor symptoms) occurs while clinical signs of disease are not evident, but underlying neurodegeneration has started and progressed [7]. Clinical studies have shown that rapid eye movement sleep behavior disorder (RBD), depression, olfactory dysfunction, constipation, and autonomic dysfunction may be present during this period [8,9]. The 2019 Movement Disorders Society diagnostic criteria for prodromic PD have added other new markers (such as diabetes mellitus and physical inactivity), facilitating a web-based calculation of prodromic risk [10]. Effective therapy alleviates the manifestations of the disease, moving the symptomatic progression curve to the right by several years, but does not affect the disease process as such [11]. No therapy has yet been

proven to be disease-modifying [12]. Epidemiological as well as interventional studies indicate that the plant-based diet has the potential to prevent and treat PD. There are pathophysiological reasons that make this likely to be true.

Epidemiology

The etiology of PD involves both genetic and environmental factors. Although PD is generally an idiopathic disorder, there are a minority of cases (10–15%) that report a family history, and about 5% have Mendelian inheritance [13]. Furthermore, an individual's risk of PD is partially the product of as-yet-poorly-defined polygenic risk factors [13]. The genes that have been found to potentially cause PD are assigned a "PARK" name in the order they were identified. To date, 23 PARK genes have been linked to PD [14].

There is a growing body of epidemiological evidence to support the case that diet impacts (positively or negatively) the development of neurodegenerative diseases such as PD, so interest has been growing in the influence of food and nutrients on the development of PD. The Western diet is among the greatest risk factors for developing neurodegenerative diseases such as PD, [15,16] whereas nicotine and caffeine use are associated with decreased risks [17]. Age-adjusted prevalence rates of Parkinson's disease tend to be relatively uniform throughout Europe and America. However, sub-Saharan black Africans, rural Chinese, and Japanese, groups whose diets tend to be quasi-vegetarian, appear to enjoy substantially lower rates. Since current PD prevalence in African-Americans is little different from that in whites, environmental factors are likely to be responsible for the low PD risk in Black Africans [18]. Consumption of high quantities of animal saturated fat has been widely reported to be associated with increased risk of developing Parkinson's disease [19]. Three recent case control studies conclude that diets high in animal fat or cholesterol are associated with a substantial increase in risk for Parkinson's disease. However, fat of plant origin does not appear to increase risk, [18, 20]and may even lower it [21]. Dairy product consumption and drinking milk may increase one's risk of PD independently of calcium intake [22-25] particularly in men [26]. A positive association between milk consumption and PD risk was also observed in women in one study [27]. In contrast, studies have also shown that diets with high vegetable and fruit intake are associated with a decreased risk for PD, particularly in men [18].

Insulin resistance and diabetes accelerates deterioration of motor function, while inhibiting the effectiveness of levodopa treatment in PD patients [28]. Multiple epidemiological studies suggest that body mass index (BMI), insulin resistance, and diabetes increase the risk of PD [29]. For example, a study of over 45,000 people in Finland demonstrated a positive association between BMI and risk of PD, [30] and a study in Denmark showed that having diabetes increased the risk of PD by nearly 40% [31]. The progression of neuropathology in PD may be accelerated by insulin resistance, as suggested by a study showing that dementia is associated with insulin resistance in PD patients [32]. There are also environmental contributions to the risk of PD. Pesticide, herbicide, and heavy metal exposures are linked to an increased risk of Parkinson disease in some epidemiologic studies [17]. Based on several comprehensive epidemiological studies, pesticide exposure appears to be a particular risk factor for Parkinson's disease [33-35]. The data supporting a role for organochlorines in increasing the risk of PD continue to grow, including a recent family-based case-control study that demonstrated such an association [36].

Pathophysiology

Among the various neuronal types that degenerate in this disease, there is little doubt that the degeneration or loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc) is responsible for the characteristic motor symptoms and drives symptomatic therapies [37,38]. The hallmark lesions called Lewy bodies, eosinophilic inclusion bodies, are produced by the progressive accumulation of protein inclusions containing α-synuclein and ubiquitin in the cytoplasm of selected neurons, which leads to their death by necrosis and/or apoptosis. Lewy bodies are present mainly in the surviving neurons and are considered as the biological marker of neuronal degeneration in PD [3]. While the etiology of PD remains poorly understood, several underlying pathophysiological mechanisms such as oxidative stress, neuroinflammation, iron dysregulation, mitochondrial dysfunction, excitotoxicity, loss of neurotrophic factors, glial activation, and endoplasmic reticulum stress, as well as protein misfolding and dysfunction in their degradation, have been credited as significant pathways for the development of therapeutic approaches [39,40].

Accumulating evidence indicates that oxidative damage and mitochondrial dysfunction contribute to the cascade of events leading to degeneration of dopaminergic neurons [41-45]. Furthermore, evidence suggests that possible modification of the gut microbiota may be involved in the pathogenesis of PD, inducing immune cell activation and neuroinflammation of the central nervous system [46]. Organochlorine compounds exhibit chemical properties, toxicokinetic features and temporal and geographic-use patterns that make them reasonable candidates to contribute to the incidence of PD [36]. The organochlorine pesticide dieldrin is an extremely persistent organic pollutant. It does not easily break down in the environment, and tends to bioaccumulate as it is passed along the food chain. Long-term exposure has proven toxic to a very wide range of animals including humans, far greater than to the original insect targets [47].

Dieldrin has been found in human PD postmortem brain tissues, suggesting that this pesticide has potential to promote nigral cell death. Although dieldrin has been banned, humans continue to be exposed to the pesticide through contaminated dairy products and meats, due to the persistent accumulation

of the pesticide in the food chain including farm animals [47]. People exposed to dieldrin are at about a 250 percent higher risk of developing Parkinson's disease than the rest of the population [48,49]. Since organochlorine compounds bioaccumulate in animal tissue, those following a vegan diet will have a much lower level of exposure.

Inflammation

In 1988, McGeer's research team suggested that inflammation could be the first pathogenic mechanism of PD [50]. At the same time, it has been observed that the use of non-steroidal anti-inflammatory drugs (NSAID) decreases the risk of PD, and this could be considered as a proof of inflammogenic characteristics of the disease [51].

While neuronal death has been described as evidence of ongoing Central Nervous System (CNS) inflammation [52], several scientific reports documented microglial activation, cytokine production, and the presence of autoantibodies, univocally indicating inflammatory processes in PD [53-56]. In vitro assays employing a dopaminergic neuron model showed some membrane proteins to be targeted by antibodies present in cerebrospinal fluid (CSF) of affected patients [57]. Research performed on post-mortem excised brains revealed higher concentrations of cytokines and proapototic proteins in the striatum and CSF of PD patients compared to levels found in healthy controls, pointing at inflammation as a constant element of the disease [58].

Through a further immunohistological study, McGeer et al. discovered several alterations in striatal microglial cells of patients with PD, which appeared to be activated by an increased synthesis of proinflammatory cytokines [59]. Nonetheless, it remains to be explained whether inflammation represents the first cause determining neurodegeneration, or if it results from a selective damage process and cell degeneration.

A plant-based diet has been shown to reduce markers of inflammation such as CRP. Lower levels of hs-CRP were found in those following a vegetarian diet for more than 2 years [60,61]. An interventional study found that after 8 weeks on a vegan diet, hs-CRP was reduced 32%, even more than the American Heart Association diet [62].

Oxidative Stress

Oxidative stress is a well-accepted concept in the etiology and progression of Parkinson's disease [63]. Oxidative stress plays an important role in the degeneration of dopaminergic neurons in PD. Disruptions in the physiologic maintenance of the redox potential in neurons interfere with several biological processes, ultimately leading to cell death. Evidence has been developed for oxidative and nitrative damage to key cellular components in the PD substantia nigra [64]. In addition to PD, several other neurodegenerative disorders including Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis are associated with oxidative stress as well, despite having distinct pathological and clinical features, [65] suggesting that oxidative stress is a common mechanism contributing to neuronal degeneration [66,67].

The extensive production of Reactive Oxygen Species (ROS) in the brain may provide an explanation for the magnitude of the role that these reactive molecules play in PD. The brain consumes about 20% of the oxygen supply of the body, and a significant portion of that oxygen is converted to ROS [68]. ROS can be generated in the brain from several sources, both in neurons and glia, with the electron transport chain being the major contributor at the mitochondrial level [69,70]. As one of the main sites of ROS production, mitochondria are particularly susceptible to oxidative stress-induced damage. Unlike nuclear DNA, mitochondrial DNA (mtDNA) are unprotected by histone proteins and therefore are easy targets of oxidation [71]. ROS production and mtDNA damage have been shown to increase with age, up to 10–20 folds higher than in nuclear DNA [72,73].

A plant-based diet reduces oxidative stress through its rich supply of antioxidants [74,75]. Phytonutrients (also called phytochemicals), naturally occurring protective chemicals found in foods of plant origin and in plant based diets, are reported to have antioxidant properties [75]. Parkin is an E3 ubiquitin ligase that promotes mitophagy of damaged depolarized mitochondria while also boosting mitochondrial biogenesis, thereby helping to maintain efficient mitochondrial function. Boosting Parkin expression in the substantia nigra (SN) with viral vectors is protective in multiple rodent models of PD. Conversely, homozygosity for inactivating mutations of Parkin results in early-onset PD.Moderate-protein plant-based diets, relatively low in certain essential amino acids, have the potential to boost Parkin expression by activating the kinase GCN2, which in turn boosts the expression of ATF4, a factor that drives transcription of the Parkin gene [76].

Microbiome Dysbiosis

A pathological characteristic for PD is the presence of cytoplasmatic eosinophilic alpha-synuclein inclusions in the form of Lewy bodies in cell somata and Lewy neurites in axons and dendrites [77-79]. The alpha-synuclein protein is generally expressed in the CNS, mainly in presynaptic terminals. It is thought to be involved in the regulation of neurotransmission and synaptic homeostasis [80,81]. Studies suggest that it plays a role in modulating the supply and release of dopamine. There is some evidence that proinflammatory dysbiosis is present in PD patients,and could trigger inflammation-induced misfolding of alpha-synuclein and development of PD pathology [82]. It has been suggested that alpha-synuclein could act like a prion protein during PD pathogenesis. In this theory, pathologic misfolded alpha-synuclein is an 'infectious' protein, spreading pathology by forming a template that seeds misfolding for nearby alpha-

synuclein protein, turning the previously healthy protein into a pathogenic protein [83,84]. Emerging evidence has indicated that gut microbiota dysbiosis plays a role in several neurological diseases, including PD [79]. Evidence suggests that the enteric nerves are involved in the PD pathological progression towards the central nervous system. In the course of PD, the enteric nerves and parasympathetic nerves are amongst the structures earliest and most frequently affected by alpha-synuclein pathology [85]. One of the most common non-motor symptoms of PD is gastrointestinal dysfunction, usually associated with alpha-synuclein accumulations and low-grade mucosal inflammation in the enteric nerves.

The gut-brain axis is believed to be a bidirectional signaling pathway between the gastrointestinal tract and central nervous system [86-89]. The role of the vagus nerve and its branches in the pathogenesis of PD has recently been brought into focus. A retrospective study demonstrated that individuals undergoing bilateral truncal vagotomy and super selective vagotomy were at a reduced risk of developing PD as compared to the general population. This observation supports a strong association of vagal nerve fibers with the pathogenesis of PD [90].

PD pathogenesis may be caused or exacerbated by dysbiotic microbiota-induced inflammatory responses that could promote alpha-synuclein pathology in the intestine and the brain or by rostral to caudal cell-to-cell transfer of alpha-synuclein pathology caused by increased oxidative stress (due to an increase in pro-inflammatory bacteria) [79]. Dietary components might influence the gut-brain axis by altering microbiota composition or by affecting neuronal functioning in both the enteric nerves and the central nervous system (CNS) [91]. Recent research has shown that intestinal microbiota interact with the autonomic and central nervous system via diverse pathways including the enteric nerves and vagal nerve [85].

There has been detection of abnormalities in the GI microbiome (gut dysbiosis) in patients with PD [92, 93, 94] and the discovery of inflammatory changes in the intestinal mucosa, enteric nervous system, vagus nerve, and the brain of patients with PD [95]. One study has provided evidence that bacterial flora causes enteric inflammation in PD, and further reinforces the role of peripheral inflammation in the initiation and/or the progression of the disease [96]. Additionally, intestinal permeability was increased and beneficial metabolites of microbiota function, such as short chain fatty acids (SCFA), were lower in those with PD compared to healthy controls [97]. SCFA butyrate has anti-inflammatory properties thought to be owing to an epigenetic mechanism or to the activation of SCFA receptors, leading to anti-inflammatory effects, anti-microbial effects, and to a decreased intestinal barrier leakiness [98-100]. PD patients show an increased intestinal permeability that correlates with intestinal alpha-synuclein accumulation [97]. The increased intestinal permeability and the translocation of bacteria and inflammatory bacterial products

such as lipopolysaccharides (LPS) might lead to inflammation and oxidative stress in the GI tract, thereby initiating alpha-synuclein accumulation in the enteric nerves [97,101,102]. In addition, gut-derived LPS can promote the disruption of the blood brain barrier, [103] and thus facilitate neuroinflammation and injury in the SN that is triggered by dysbiosis.

It is not possible to determine for sure if changes in the gut microbiota are a cause or a consequence of PD pathogenesis. However, it might still play a role in neuronal loss by perpetuating inflammatory cascades and oxidative injury in the brain through a lipopolysaccharide-mediated mechanism [91]. The LPS from pro-inflammatory intestinal flora bacteria can induce a chronic subclinical inflammatory process.

The importance of fiber

The term prebiotics was first introduced in 1995 by Gibson and Roberfroid as a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health [104]. Since then, the original definition has been revised several times and recently broadened to 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' [105]. This should not be confused with probiotics, defined as live microorganisms that confer a health benefit on the host when administered in adequate amounts [106].

The difference in gut microbiota composition between individuals following vegan or vegetarian diets and those following omnivorous diets is well documented. One way that a plant-based diet appears to be beneficial for human health is by promoting the development of more diverse and stable microbial systems [91]. Such diets are high in dietary fiber and fermentable substrate (i.e. non digestible or undigested carbohydrates), which are sources of metabolic fuel and encourage the growth of species that ferment fiber into metabolites as short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, that may be used by the host. These end products may have direct or indirect effects on modulating the health of their host [107]. Apart from being the preferred energy source for colonic epithelial cells, butyrate is involved in anti-inflammatory, enteroendocrine and epigenetic mechanisms that influence colonic and systemic health, including improved immunity against pathogens, blood–brain barrier integrity, brain function, provision of energy substrates, and regulation of critical functions of the intestine [108,109]. Fecal SCFA concentrations have been found to be significantly reduced in PD patients [110].

Phytochemicals

A plant-based diet includes phytochemicals that have a therapeutic effect, including flavonoids, nicotine and caffeine. Flavonoids are the most common groups of polyphenols in human diet [111]. Many plant-based foods and beverages are rich in flavonoids, such as berry fruits and citrus fruits [112]. Flavonoids

have high antioxidant capacity [113]. They have been shown to modulate oxidative-related enzymes and regulate mitochondrial function in neurons [111, 114]. These findings point to a potential protective role of flavonoids in PD. In experimental studies, administration of flavonoids or flavonoid-rich foods (eg. berry fruits) protected dopamine neurons from oxidative damage and apoptosis and inhibited formation of α-synuclein fibrils [115].

Nicotine

Nicotine is the addictive phytochemical in tobacco, which is derived from plants in the Nicotiana species of the Solanaceae family. Nicotine accounts for approximately 95% of the total alkaloid content of tobacco, while the structurally-related nornicotine and anatabine are the most abundant minor pyridine alkaloids, accounting for 4 to 5% of total alkaloids [116]. Other pyridine alkaloids in tobacco, such as anabasine, anabaseine, and cotinine, are present in smaller amounts [117].

Nicotine and all minor tobacco alkaloids have been shown to be pharmacologically active upon binding to several nicotinic acetylcholine receptors (nAChRs) [118]. Tobacco nAChR agonists such as nicotine, anatabine, anabasine, anabaseine, and cotinine, display protective effects in animal models of several inflammatory conditions, including sepsis, [119] Parkinson's disease, [120] Alzheimer's disease, [121] and Inflammatory Bowel Disease [122]. In a neuro-image study, a substantial portion of nicotine receptors became occupied when exposed to relatively small amount of nicotine [123]. This notion has further been supported by the observation that long-term smoking is more important than smoking intensity in the smoking-PD relationship [124,125]. However, this does not necessarily indicate that cigarette smoking is advisable for the prevention or treatment of PD.

Besides cigarettes, nicotine is found in some common vegetables that belong to the biological family of nightshades. Other species in this family include Capsicum and Solanum, whose edible fruits and tubers include peppers, tomatoes, potatoes and eggplants. All these nightshades contain nicotine [126-130]. The nicotine levels in fresh potatoes, tomatoes and sweet peppers were only up to 10 μg/kg. Processed products contained equivalent or slightly higher levels of nicotine than fresh products (up to 34 μg/kg). Somewhat higher levels were found in fresh eggplant fruits (up to 100 μg/kg) [131]. The amount of nicotine absorbed from these foods is negligible relative to the amount obtained from active smoking [131]. However, even nicotine blood levels reached from environmental tobacco smoke exposure, much lower than that from active smoking, are sufficient to saturate a substantial portion of α4β2 nicotine receptors in the human brain [123]. Stimulation of nicotine receptors protects dopaminergic neurons in animal models of PD using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [132] or rotenone [133]. Therefore, given the strength of the association observed between PD and environmental tobacco smoke, [134] the small amounts found in solanaceae vegetables may confer a reduced risk of PD.

In a recent case-control study including 241 PD cases, each additional serving of edible solanaceae was associated with 31% lower risk of PD among never-smokers [135]. It remains unclear as to whether the observed protective effect was due to the nicotine content or other components of this group of vegetables, but consumption of all other vegetables combined showed no association. Another study showed a 30% decreased risk of PD for those in the highest quintile of nicotine in their diet [136]. Constituents of peppers other than nicotine may also be neuroprotective. Another alkyloid, anatabine, is an intriguing possibility because it has anti-inflammatory properties [136,137,138] and might be more feasibly employed as a neuroprotective chemical than nicotine, due to its longer half-life and perhaps lower toxicity and addictive potential.

Capsinoids in peppers and capsaicinoids in spicy peppers may also be neuroprotective. They activate transient receptor potential cation channel subfamily vanilloid member 1 (TRPV1) receptors [139]. These receptors are in the substantia nigra, and they and capsaicin may affect survival of midbrain dopaminergic neurons [140,141]. Cruciferous vegetables such as cauliflower, cabbage, and broccoli, are another group of vegetables rich in antioxidants with neuroprotective capacity. For example, sulforaphane and erucin are potent, naturally occurring, isothiocyanates found in cruciferous vegetables with antioxidant properties. Treatment with sulforaphane ameliorated motor deficits, and protected dopaminergic neurons, in a 6-OHDA mouse model of PD [142]. Similarly, erucin provided neuroprotective effects by preventing oxidative damage induced by 6-OHDA in an in vitro model [143]. Both sulforaphane and erucin appear to be promising neuroprotective agents in chronic neurodegenerative diseases [144]. Taken together, these findings highlight the effects of some vegetables, fruits, and constituents they contain, as having neuroprotective potential.

Caffeine

The consumption of coffee or caffeinated food is associated with the reduction of the risk of PD. Patients with PD are less frequent habitual consumers of caffeinated food [145, 22]. The consumption of either tea or coffee exhibited similar effects on the reduction of the risk of PD in a dose dependent manner [146], thus establishing caffeine as a neuroprotective phytochemical. Caffeine is an adenosine A2A receptor antagonist [147]. Different types of adenosine receptors (A1, A2A, A2B, and A3) are widely distributed in the brain. Adenosine A2A receptors are coupled with G-proteins and exclusively expressed in dopaminergic neurons. The activation of adenosine A2A receptors causes an increase in intracellular cAMP levels and the extracellular release of glutamate, resulting in neural excitotoxicity [148]. The neuroprotective effects of caffeine involved the antagonism of the adenosine A2A receptor, down-regulating the down streaming

phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway and avoiding excessive calcium releasing-related neurotoxicity and neuroinflammation [149], which has been experimentally demonstrated in several in vivo models of PD [150-153].

Interventional studies

In spite of extensive research, the pharmacotherapeutic options for Parkinson's disease are limited to those which offer only symptomatic relief and cannot prevent the disease progression, so there is still need for effective disease-modifying agents for PD [154,155].

The pharmacotherapeutic approach with antioxidants is gradually being preferred as disease-modifying strategies in neurodegenerative diseases, including PD [155-160]. Chronic consumption of anti PD drugs by PD patients, and their reduced efficacy, are leading researchers to look for probable synthetic or natural compounds and dietary treatment for the PD therapeutics. A number of pharmacological, genetic, and clinical studies, including postmortem PD brain studies, show that mitochondrial defects, increased reactive oxygen species (ROS), and induction of inflammatory mediators play a very critical role in the development of PD [161,162]. Accordingly, oxidative stress and inflammatory processes are the major therapeutic targets of intervention to delay the development and progression of PD [154].

The concept of neuroprotection referring to the prevention of dopamine cell death, and hence to retarding or halting disease progression, appears to be a promising strategy. It is convincing that naturally occurring molecules, possessing antioxidant and anti-inflammatory activities along with other pharmacological properties, could be effective in preventing or halting the neurodegenerative processes [158-160]. Various substances exhibiting anti-inflammatory, antioxidant, and metal chelating activity in the central nervous system (CNS) have been tested for use to facilitate the management of PD. In this context, natural polyphenols have recently raised much attention [163]. Numerous studies have indicated the neuroprotective effects of natural polyphenols including epigallocatechin, quercetin, baicalein, resveratrol, luteolin, curcumin, puerarin, genistein, and hyperoside naringin, against dopaminergic neuronal death with relatively safe with uncommon, mild or transient side effects [164].

Another potential treatment is the use of ferulic acid (FA). FA is an important component of widely used medicinal herbs and belongs to the family of hydroxycinnamic acid. Pure form of FA appears as yellowish powder, and it has structural resemblance to curcumin, one of the well-studied natural molecules with potent neuroprotective effects. FA is highly abundant in the leaves and seeds of many plants, especially in cereals such as brown rice, whole wheat, and oats. It has been credited with many pharmacological properties including neuronal progenitor cell proliferation, anti-inflammatory, antioxidant, and neuroprotective activities [165-174]. The neuroprotective effect of FA has been reported in several experimental studies including brain injury, spinal ischemia, and Alzheimer-like pathology [168,169,171], so it is reasonable to assume that it could also have a therapeutic effect for PD patients.

Food also appears to affect the pharmacokinetic and pharmacodynamic of levodopa, a prodrug of dopamine which remains the most effective agent to alleviate motor dysfunction in Parkinson's disease. L-Dopa can enter the brain and be decarboxylated to dopamine only after crossing the blood–brain barrier by means of a specific saturable carrier system (the large neutral amino acid transporter, LAT). At this level, it competes with some dietary essential amino acids (the large neutral amino acid, LNAA, including tyrosine) which block L-dopa entry into the brain, even if blood concentrations of the drug are adequate [175].

To avoid the risk of nutritional deficiencies linked to an extreme restriction in total protein intake, some doctors use the "protein redistribution diet." This intervention consists of a normoproteic diet (protein calories about 10–15% of total calories, about 0.8–1.0 g/kg/day) with the main protein intake concentrated in the evening meal, in order to limit the negative interaction of LNAA on L-dopa response during daytime, and let the negative effect act at night-time during sleep [176]. An effect of this intervention was noticed within one week in patients who had previously benefited from L-dopa therapy [177,178]. The effect of the protein distribution lasted for years [179].

Some researchers have described an increased bioavailability of L-dopa by increasing insoluble fiber consumption [179,180]. A study was designed to ascertain whether a plant-food normoproteic protein-redistributed diet can be as effective as a protein-redistributed omnivorous one in improving motor performances in PD patients in the short term [180]. This study compared the effect of a plant-based diet with an omnivorous diet on motor performance. After 4 weeks, patients following a plant-based diet showed a significant reduction (Mann–Whitney test) in the Unified Parkinson's Disease Rating Scale, total score (47.67 vs. 74.46) and sub-score III motor performances (25.42 vs. 46.46), and the modified Hoehn and Yahr Staging Scale (1.96 vs. 3.15). The patients in this study had L-dopa daily dosage of over 350 mg, but under 850 mg, their age was over 50 years, and their BMI was over 18.5 but under 30. Two thirds of the plant protein was consumed at night [180].

So a plant food (vegan) diet can be a convenient way to conjugate the positive effect of limited protein intake and high fiber intake without limiting total food amount. Due to its high fiber content, a plant-food diet can also potentially raise levodopa bioavailability by reducing the phenomenon of constipation [181]. Another intervention that was tried was the use of omega-3 fatty acids and Vitamin E. In a randomized double-blind placebo-controlled

clinical trial, patients received either 1000 mg omega-3 fatty acids from flaxseed oil plus 400 IU vitamin E supplements for 12 weeks, or a placebo. Unified Parkinson's disease rating stage (UPDRS) were recorded at baseline and after 3 months of intervention. After 12 weeks of intervention, omega-3 fatty acids and vitamin E co-supplementation led to a significant improvement in UPDRS. Furthermore, co-supplementation decreased high-sensitivity C-reactive protein (CRP) and increased total antioxidant capacity (TAC) and glutathione (GSH). Insulin resistance improved along with beta cell function [182]. The omega-3 fatty acids were from flaxseed oil, showing that animal sources of omega-3 such as fish are not required.

Riboflavin-sensitive mechanisms involved in PD may include glutathione depletion, cumulative mitochondrial DNA mutations, disturbed mitochondrial protein complexes, and abnormal iron metabolism [183]. Another study combined the elimination of red meat with riboflavin supplementation. All PD patients received 30 mg riboflavin orally at about 8-hr intervals (90 mg/day) and their usual symptomatic medications. This dosage was used to avoid decreased absorption associated with higher doses or shorter intervals between administrations [183]. Due to the renal excretion of riboflavin, the treatment was only initiated after confirmation of normal blood levels of creatinine (0.5-1.4 mg/dl) [154].

Because the PD patients had a higher consumption of red meat (beef and pork) than sex-matched controls (19 healthy non-consanguineous relatives or neighbors of similar age recruited for controlling the dietary habits), all PD patients were required to eliminate all red meat from their diets. The symptomatic drugs for PD in use included L-Dopa with carbidopa (200/50 mg tablets), L-Dopa with benserazide hydrochloride (200/50 mg tablets), biperiden (2 or 4 mg tablets), amantadine hydrochloride (100 mg tablets), selegiline (5 mg tablets), and pramipexole (0.25 or 1.0 mg tablets) taken alone or in diverse combinations. The treatment paradigm when the study began, with symptomatic drugs for PD for each patient, was maintained. All patients who completed 6 months of treatment showed improved motor capacity during the first three months, and most reached a plateau while 5/19 continued to improve in the 3- to 6-month interval. Their average motor capacity increased from 44 to 71% after 6 months, increasing significantly every month compared with their own pretreatment status (P < 0.001, Wilcoxon signed rank test). Discontinuation of riboflavin for several days did not impair motor capacity and yellowish urine was the only side effect observed [183].

People with PD tend to be at greater odds of having a CoQ10 deficiency, an antioxidant that is important for the detoxification system, which may be partially responsible for their toxic burden [184]. Several high-quality studies have shown that supplementation with 100–1,200 mg of CoQ10 daily, particularly larger dosages, reduces inflammatory markers and improves motor symptoms [185-189].

Case Study

Increasing evidence suggests that Parkinson disease consists of heterogeneous subtypes. Subtypes have implications for diagnosis, prognosis, and expected treatment response. Initial sub-typing focused on motor features [190,191]. Definitive diagnoses for both Parkinsonisms and Parkinson's disease can only be done via an autopsy [192]. A case study was done on a patient with Parkinsonism that includes Parkinson's disease in the differential diagnosis [193]. A 64-year-old man had depression since his 30's that was treated with the MAO inhibitor tranylcypromine. At age 51, he had onset of urinary frequency/urgency and erectile dysfunction. About 4 years later, he developed bradykinesia, bilateral rigidity, start hesitation, and sudden transient freezing. He did not have tremor and there were no vascular risk factors. An MRI of the brain was unremarkable. This patient was diagnosed with levodopa-responsive Parkinsonism, characterized mainly by start hesitation, gait freezing, and prominent autonomic dysfunction. The differential diagnosis included PD with dysautonomia or multiple system atrophy. Vascular parkinsonism was unlikely given the absence of both vascular risk factors and vascular abnormalities on brain imaging. He was tried on trihexyphenidyl and amantadine with no response and experienced only modest benefit from dopamine agonists.

The patient changed his diet to avoid protein during breakfast and lunch, and found that he had a better, more predictable response to levodopa. After 2 months, he adopted a vegan diet and since then has experienced steady and dramatic improvement in his motor symptoms. His gait has returned to almost normal, with near complete resolution of freezing and start hesitation. He now runs and ice skates, activities nearly impossible previously, with no difficulty. He was able to reduce levodopa from 2175 mg/day to 1305 mg/day, although symptoms recur when levodopa is reduced further [193]. A protein redistribution diet (PRD) in this patient was useful, probably by reducing competition from diet-derived amino acids for transport across the intestinal and the blood-brain barrier, as has been described previously [194]. More remarkable, however, was his response to a vegan diet that included only organic, plant-based foods and eliminated all animal-derived products such as eggs, cheese, and other milk products.

The benefits of a vegan diet may be derived from its protein-sparing qualities, which may be stricter and more consistent than the protein redistribution diet he used. A plant-based diet is also generally rich in fiber, which may improve bowel motility, thereby promoting the bioavailability of levodopa. Although its influence on levodopa pharmacokinetics is one mechanism for the fairly quick clinical benefit produced, a vegan diet may have other

benefits for PD that contributed to the patient's improvement. This includes an antioxidative effect, with its high levels of antioxidants slowing the loss of surviving dopaminergic neurons, thus retarding progression of the syndrome. Other benefits are the anti-inflammatory properties, caloric reduction, promotion of vascular health and aiding blood-brain barrier transport of L-dopa [195,18] . All of these actions are relevant to the current understanding of factors that influence neurodegeneration in PD.

Clinical Considerations

The incidence of Parkinson's disease rapidly increases over the age of 60 years, with only 4% of the cases being under the age of 50 [196]. The prevalence of chronic diseases such as type 2 diabetes, [197] coronary artery disease, [198] prostate [199] and colon cancer [200] increases during this time as well. Hence comorbidities will be common. A plant-based diet protects against chronic oxidative-stress-related diseases. Dietary plants contain variable chemical families and amounts of antioxidants. Plant antioxidants may contribute to the beneficial health effects of dietary plants [201]. On average plant foods provide 11.57 mmol/100gm antioxidant content, while animal foods provide only on average 0.18 mmol/100gm [201].

Recently, clinical and scientific attention has shifted to treating additional nonmotor symptoms that in the past have often passed unheeded [202]. Constipation is one of the most frequent non-motor symptoms in the autonomic system [203-204] and gastrointestinal disturbance of PD [205]. Between 50% and 80% of PD patients suffer from constipation [205-209]. It has been reported that constipation can precede motor symptoms by as much as 20 years [210]and people with constipation may have a relatively high risk of developing PD [211]. Accordingly, constipation may predict the occurrence of PD. However, PD patients may not talk about their symptom of constipation actively, leading to this problem not being reported in time [212].

Underlying causes for constipation in PD are multifaceted. Besides physical weakness, lifestyle risks such as lack of fiber and reduced fluid intake may substantially promote its emergence [213]. Moreover, side effects of medication and disease-related pathomechanisms have been identified [214-216]. Regarding the latter, two usually concomitant alterations require distinction: slow intestinal transit and outlet obstruction. Increasing evidence indicates that delayed colonic transit in PD stems from disordered central, as well as peripheral, parasympathetic system dysregulation [217]. On top of functional impairment, psychosocial distress increases with constipation in PD, strongly suggesting a negative impact on the quality of life [212, 218-220]. These manifold characteristics of PD-associated constipation highlight an urgent demand for efficacious treatment. Comprehensive and valuable reviews have emerged on the topic of PD-related constipation in recent years [221-223].

In one study, the effects of a diet rich in insoluble fiber (DRIF) on motor disability, and the peripheral pharmacokinetics of orally administered L-dopa, in Parkinsonian patients with marked constipation were analyzed [179]. A useful effect of a DRIF on plasma L-dopa concentration and motor function was found. The greatest effect on the plasma L-dopa levels was found early (at 30 and 60 min) after oral administration. There was a relationship between the improvement of constipation and the higher bioavailability of L-dopa. DRIF can be a coadjuvant treatment in patients with Parkinson's disease.

In PD subjects with confirmed constipation, adding psyllium to the diet increased stool frequency and weight, but did not alter colonic transit or anorectal function. Psyllium produced both subjective and objective improvements in constipation related to PD [209]. Prospectively obtained stool diaries should be employed to confirm constipation in PD.

Discussion

There are no disease modifying drugs to treat Parkinson's disease. This makes prevention all the more important. A plant-based diet can help reduce the risk of Parkinson's disease. In particular, several phytochemicals present in plant foods help reduce the risk of Parkinson's disease. The increased fiber in a plant-based diet promotes butyrate-producing flora thus reducing inflammation, and it treats constipation, a risk factor for Parkinson's disease. Eliminating meat from the diet plays its part in reducing the risk. Therefore, both the presence of plant foods and the absence of meat and dairy combine to reduce risk.

Treatment with a plant-based diet can enable the dosage of medications used to treat the symptoms to be reduced. This may be especially advantageous in treating constipation caused by anticholinergics. The long-term benefit of a plant-based diet in slowing the progression of Parkinson's disease should be researched. Its efficacy in treating nonmotor symptoms should also be researched further.

Since Parkinson's disease often occurs later in life, the fact that a plant-based diet can reduce the risk, as well as treat common comorbidities such as type 2 diabetes, cardiovascular disease, prostate and colon cancer, makes prophylaxis with it all the more valuable. Treating the Parkinson's disease patients with a plant-based diet has no contraindications or adverse reactions. It offers a safe treatment as an adjunct to treatment with standard pharmacotherapy. A plant-based diet is affordable and can also relieve the financial stress on the Parkinson's disease patient which is considerable.

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