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Narrative Review

The Damages Made by *Helicobacter Pylori* on Parkinson and Emerging Role of Nutrition in Parkinson's Disease

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Abstract

Parkinson's disease (PD) is a widespread degenerative illness impacting the human central, peripheral, and gastrointestinal nervous systems. The underlying pathological process progresses slowly but relentlessly and involves multiple neuronal systems. The disease is the consequence of changes in the neuronal cytoskeleton developing in only a few susceptible types of nerve cells. The cardinal features of PD are bradykinesia, rigidity, tremor, and postural instability. There are a number of neurologic conditions that mimic the disease, making it difficult to diagnose in its early stages. Physicians who rarely diagnose PD should refer patients suspected of having it to physicians with more experience in making the diagnosis, and should periodically reevaluate the accuracy of the diagnosis. Several studies have shown associations between PD risk and individual foods and nutrients with inconsistent results is now clear that genetic susceptibility and environmental factors play a role in disease etiology and progression. Because environmental factors are involved with the majority of the cases of PD, it is important to understand the role nutrition plays in both neuroprotection and neurodegeneration. *Helicobacter pylori* has been implicated in the pathogenesis of PD. Its eradication, in a randomized placebo-controlled trial, improved PD inactive *Helicobacter* species zoonosis might explain excess mortality from PD and non-Hodgkin lymphoma in livestock, but not arable, farmers. Indeed, Helicobacter is causally-associated with gastric lymphoma.

Keywords: Parkinson Disease, Nutrition, Dietary Pattern, *Helicobacter pylori*, Interaction, Levodopa, Epidemiology

Introduction

Parkinson disease (PD) is a progressive neurodegenerative disorder that is pathologically defined by degeneration of the dopaminergic neurons in the substantia nigra and development of lewy bodies in the residual dopaminergic neurons.[1] Pathologic changes may be detected up to 20 years before the onset of motor symptoms, and are accompanied by a clinical prodrome of nonspecific symptoms such as hyposmia, constipation, and fatigue.[2] the disease affects approximately 1 percent of persons older than 60 years, and up to 4 percent of those older than 80 years. PD is a neurodegenerative disease that usually develops late in life and is characterized by the loss of dopaminergic neurons in the substantia nigra pars compacta. Most cases of PD are idiopathic since their cause is unknown. A growing body of evidence suggests that nutrition may play an important role in pd. Epidemiological and biochemical studies have recently identified promising components in certain food groups that may elicit neuroprotection in pd. It has been known for more than a century that bacteria are present in the human stomach. About 25 years ago, Barry Marshall and robin warren described the successful isolation and culture of a spiral bacterial species, later known as *Helicobacter pylori*, from the human stomach. *H. pylori* colonies the gastric mucosa and upper duodenum by adhering to, and penetrating into, the mucous layer of the human gastric epithelium.

Parkinson Disease

Neurological disorders are now the leading source of disability globally, and the fastest growing neurological disorder in the world is PD. From 1990 to 2015, the number of people with PD doubled to over 6 million. For most of human history, Parkinson has been a rare disorder. Several studies have shown associations between PD risk and individual foods and

nutrients with inconsistent results. We examined associations between dietary patterns and risk of PD in the Health Professionals. Dietary patterns with a high intake of fruit, vegetables, legumes, whole grains, nuts, fish, and poultry and a low intake of saturated fat and a moderate intake of alcohol may protect against PD. Benefits of a plant-based dietary pattern including fish to PD merit further investigation. Genetic susceptibility and environmental factors that mediate mitochondrial dysfunction, inflammation, abrogation of the autosomal -lysomal autophagy system, and endoplasmic reticulum stress play a role in disease development. Degenerative parkinsonian disorders can be inherited or sporadic, but they all have selective loss of dopaminergic neurons in the substantia nigra that project to the basal ganglia. Within the substantia nigra, the ventrolateral cell groups are most vulnerable, while dorsal and medial cell groups are more resistant. The biological basis for selective vulnerability of dopaminergic neurons may reside in pacemaker-like properties of these cells, leading to frequent intracellular calcium transients. Calcium buffering may be relatively deficient in A9 neurons compared with A10 neurons, leading to cellular stress and eventual disruption of cellular homeostasis. Cell death is associated with disruption of nuclear membrane integrity and release of proaggregant nuclear factors, such as histones, that may trigger α-synuclein aggregation. Once aggregation begins, it may subsequently spread to other cells by direct or indirect means. Propagation of abnormal forms of α-synuclein can be modeled in cellular and animal systems and it is the most popular hypothesis to explain the progressive involvement of select neuronal systems in PD.[1]

The Symptoms of Parkinson's Disease

PD is a progressive disorder of the nervous system that affects movement. Symptoms start gradually and sometimes start with just a small tremor in one hand, which the person barely notices. In addition to tremors, which are very common, this disorder usually causes stiffness or slowness of movement. The signs and symptoms of PD can be different for everyon.[3] Initial symptoms may be mild and unnoticeable. Symptoms often start on one side of the body and are usually more severe on the first side, even after symptoms develop on both sides. In the early stages of PD, facial expression may be a low expression of this disease. Hands may not move when walking. The person's speech may be slow or slurred. The symptoms of PD get worse as the disease progresses and over time (Figure 1).

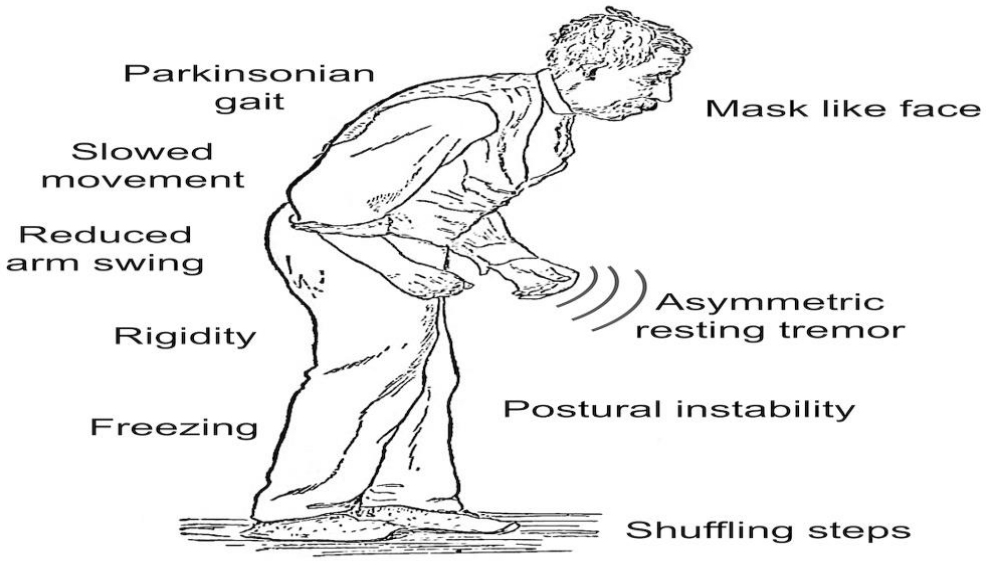

Figure 1. The Symptoms of Parkinson's Disease

The Motor Symptoms of Parkinson's Disease

It is estimated that up to 80% of dopaminergic cells in the nigro-striatal system are lost before the cardinal motor features of PD start to appear. the disease is usually diagnosed by the first motor symptoms. the diagnosis is based on defined criteria from the UK PD

Brain bank. Slowness of initiation of voluntary movements with progressive reduction in speed and amplitude of repetitive actions (bradykinesia) with one additional symptom, muscular rigidity, resting tremor or postural instability, are a prerequisite for the diagnosis.

The Non-Motor Symptoms of Parkinson's Disease

Before motor symptoms appear and the diagnosis is made, patients may have a variety of pre-motor symptoms. These may start as early as 10 or more years before the diagnosis and presentation with non-motor symptoms may delay the diagnosis. One study of 109 recently diagnosed patients who had not yet started treatment showed that symptoms such as a lack of emotional involvement and interest (apathy), excessive daytime sleepiness, sleep problems and constipation may occur in up to 60-70% of patients prior to the diagnosis and these symptoms were more common than in normal controls also non-motor symptoms are more common in PD patients compared to healthy controls of similar demographics. Using global non-motor symptoms questionnaires, multiple independent studies in incident and prevalent PD cohorts consistently demonstrate a high frequency of non-motor symptoms, with number of non-motor symptoms per individual patient ranging between 8-12. Increased drooling, urinary urgency, constipation, anxiety, forgetfulness or attentional problems, and decreased smell are among those reported across early PD studies.

Disturbances in Autonomic Function

Autonomic dysfunction may present prior to the diagnosis or become apparent with disease progression or be induced by medication (Koike and Takahashi 1997). All areas of autonomic function may be affected and this has been reported to affect daily life of over 50% of patients (Jost2003). The autonomic dysfunction is considered because of involvement of both the central and peripheral postganglionic autonomic nervous system. However, Kim et al., found that nocturia was also common in their control group (47.8% in controls vs. 65.2% in PD), though the sample size was small, and Muller et al., did not find a difference in increased sweating between PD patients and controls. Despite the high prevalence of the autonomic and sensory symptoms, Muller et al., found that daily activities were not affected by these symptoms in 58% of patients and they were rated as "mild" in the majority. Presence of autonomic and sensory symptoms in early and de novo PD invokes involvement of the peripheral and central nervous system consistent with the proposed progressive neurodegenerative changes by Braak.

Sleep Disturbances

The neuropathology of PD is known to affect anatomical structures and central neurotransmitters that are involved in the modulation of the physiological sleep cycle. Polysomnographic findings have shown changes in the architecture of sleep waves compared with healthy controls, but the medical treatment for different symptoms related to PD may also disrupt night-time sleep of all clinical markers, REM sleep behavior disorder (RBD) is, by far, associated with the highest PD risk. The original description of RBD as a prodromal marker reported that 38% developed PD after an average 5-year follow-up. On continued follow-up, 81% of these patients eventually developed neurodegenerative disease. Similarly, the Barcelona cohort reported a 45% risk of neurodegeneration at 5 years follow-up; this number has risen to 76% at 14-year follow-up. Sleep disturbances and excessive daytime sleepiness are common problems in PD with multi-factorial etiologies, including the disease itself, sleep-wake disruptions, and dopaminergic medications, among others. Since sedation and drowsiness are frequent side effects of dopaminergic therapies for PD, Fabbrini et al., performed a case-control study comparing the ESS and PSQI scales in de novo, untreated PD to PD patients treated with dopaminergic medications and healthy controls.

Diagnosis

The diagnosis of PD is clinical, and relies on the presence of the cardinal features of bradykinesia, rigidity, tremor, and postural instability, coupled with gradual symptom progression and a sustained response to therapy with levodopa. A physician who rarely diagnoses PD should consider referring a patient suspected of having it to a physician who has more experience with the disease to confirm the diagnosis. All patients who agreed to participate had a general and neurological interview and examination, and a questionnaire designed to detect signs and symptoms

of typical and atypical parkinsonian disorders—was completed by one of the investigators (AS). If the subject agreed to this, a video recording of the neurological signs was made. The diagnosis was made according to published criteria (see below) after review and discussion of each subject and examination of their videotape. All patients in whom a diagnosis of parkinsonism was made received a questionnaire on atypical features and symptoms of progression every three months for a period of one year. In addition, the general practitioners were asked about any new, atypical features in the eligible patients at the end of the study.

Association of *Helicobacter pylori* in among Adults with Parkinson Disease

since the first culture of *H. pylori* 20 years ago, the diagnosis and treatment of upper gastroduodenal disease have changed dramatically. Peptic ulcer disease is now approached as an infectious disease, in which elimination of the causative agent cures the condition. The role of *H. pylori* infection in gastric cancers is increasingly recognized, and its role in other diseases of the upper gastrointestinal tract is being evaluated. Enormous progress has been achieved in determining the pathogenesis of this infection. Impressive antimicrobial therapy is available, although there is still no ideal treatment, and indications for therapy continue to evolve. This review surveys scientific knowledge concerning *H. pylori* and focuses on the many aspects of this infection that are relevant. There is at present little information available about the virulence genes, physiology, or metabolism of *H. felis*, since *H. felis* is only poorly amenable to the genetic techniques used for *H. pylori*. The bacterium contains a urease gene cluster resembling that of other gastric *Helicobacter* species. as well as two flagellin genes (flaA and flaB). The latter genes have been inactivated, and this resulted in truncated flagella and reduced motility. Mutation of flaA also resulted in the inability to colonize a murine model of infection The genus *Helicobacter* belongs to the ε subdivision of the Proteobacteria, order Campylobacter ales, family Helicobacteraceae. This family also includes the genera Wolinella, Flexispira, Sulfur monas, Thiomicrospira, and Thiovulum. To date, the genus *Helicobacter* consists of over 20 recognized species, with many species awaiting formal recognition. Members of the genus *Helicobacter* are all microaerophilic organisms and in most cases are catalase and oxidase positive, and many but not all species are also urease positive[5,6] (Figure 2).

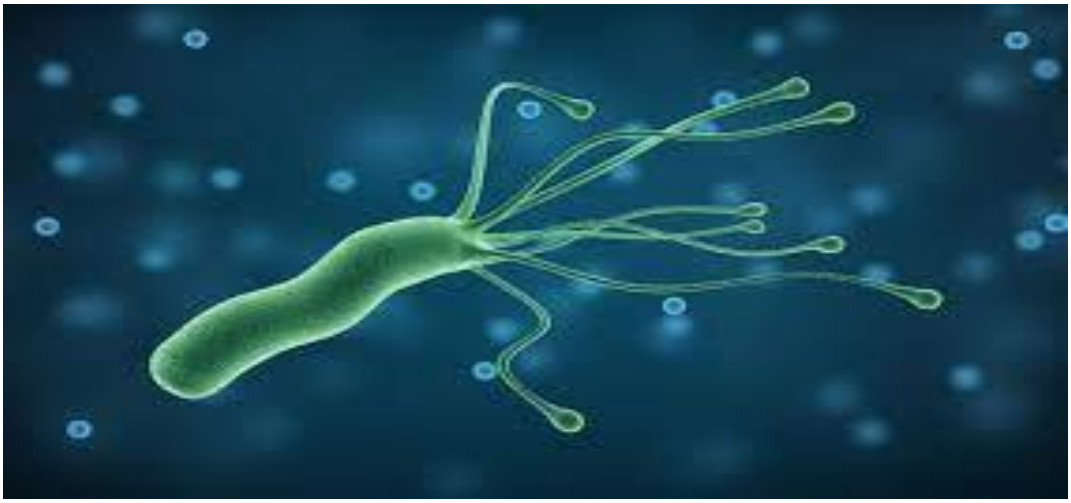

Figure 2. *Helicobacter pylori*

There is epidemiological data to suggest an increased prevalence of *H. pylori* infection in PD patients. As compared to healthy controls, one case control study has shown *H. pylori* antibodies to be 5-fold more common in PD patients over 80 years of age;[9] another study found *H. pylori* to be 3-fold more common while genetic factors clearly contribute to the development of PD, much of the variance is likely due to environmental factors that have remained enigmatic. One intriguing environmental factor for PD that has gained attention

in recent years is the gastric pathogen *H. pylori*. *H. pylori* chronically infects half the world's population, causing gastritis, ulcers, gastric adenocarcinoma and MALT lymphoma, accompanied by an array of gastrointestinal symptoms. The abundance of *H. pylori* in humans has prompted examination of the role of this pathogen in extra-gastric diseases. Remarkably, the link between PD and ulcers predates the identification of *H. pylori* as the causative agent of gastritis and ulcer formation Translational studies in humans show that autoantibodies which are elevated in *H. pylori*-positive PD patients recognize proteins that are essential for normal brain function, such as Nuclear factor I subtype A, platelet derived growth factor B and eukaryotic translation initiation factor 4A3. This suggests that *H. pylori* may cause the immune system to generate antibodies that are able to attack proteins within the brain that are required for normal brain function, thus making *H. pylori*-infected people more vulnerable to development of PD. The presence of elevated autoantibodies against proteins essential for normal neurological functions suggests that immunomodulatory properties of *H. pylori* may explain the association between the bacterium and greater PD motor dysfunction and disease severity.[2,7]

Helicobacter Interference with Levodopa Pharmacokinetics and Efficacy

H. pylori infection has been suggested to impair drug absorption. Diminished drug absorption was found in *H. pylori* infected patients under replacement therapies with iron, thyroxin and levodopa. Following eradication therapy, an improvement of drug absorption was noticed along with an inverse correlation between severity of gastric inflammation and drug absorption indices. As regards the importance of *H. pylori* for the levodopa treatment response in PD, pharmacokinetic studies of levodopa in *H. pylori*-infected subjects have been carried out in a setting of an established PD diagnosis. In a first report, fluctuations in the levodopa absorption in six *H. pylori*-infected patients with PD were observed, at difference with *H. pylori*-negative counterparts. As an extension of this, unified PD rating scale (UPDRS) scores were lower after *H. pylori* eradication. Furthermore, the 'onset' time of levodopa effects was longer, and its duration shorter in PD patients with concomitant *H. pylori* infection compared to the *H. pylori*-negative ones.[4]

The Emerging Role of Nutrition in Parkinson's Disease

Dairy product consumption and drinking milk may increase one's risk of PD independently of calcium intake, particularly in men. Nonetheless, a positive association between milk consumption and PD risk was also observed in women in one study. Preliminary research shows that individuals who consume large amounts of dairy products may often have low serum uric acid levels. Serum urate and uric acid is inversely correlated with the risk of PD and disease duration**.** Epidemiological studies found that high intake of fruits, vegetables and fish was inversely associated with PD risk. Dietary patterns, characteristic of a Mediterranean diet, are emerging as a potential neuroprotective alternative for PD. Most fruits and vegetables are rich sources of antioxidants, including vitamins A, B (riboflavin), C, and E, which are present in low levels in some PD patients. Numerous studies have reported a decrease in peroxidase, glutathione peroxidase activities, and glutathione in the SN of PD patients postmortem; suggesting metabolic failure in antioxidant mechanisms and chemical processes can lead to lipid peroxidation and parkinsonian characteristics.[8]

Omega-3

Omega-3 polyunsaturated fatty acids (PUFAs) appear to be neuroprotective for several neurodegenerative diseases. There have been no studies in PD patients that address whether omega-3s are neuroprotective, however, one study showed that supplementation with omega-3 PUFA reduced depression in PD patients. Current research focuses specifically on the omega-3 fatty acid docosahexaenoic acid (DHA). DHA is an essential factor in brain growth and development and has anti-inflammatory potential due to its ability to inhibit cyclooxygenase-2.

Caffeine

Caffeine is one of the most widely consumed substances. The health promoting benefits of caffeinated beverages is supported by numerous epidemiological studies. An inverse association between PD and coffee, and caffeine from non-coffee sources, has been reported. In general, animal studies also indicate that caffeine is neuroprotective. The administration of caffeine to maneb and paraquat-treated rodents reduced the number of degenerating dopaminergic neurons,

microglial cells and nitrite content, while normalizing expression of IL-1β, p38 MAPK, NF-kB, and TK. Acute and chronic administration of caffeine also reduced the effect of MPTP (Chen et al., 2001) and 6-OHDA treatment on striatal DA loss and motor dysfunctions in rats. Caffeine treatment partially restores DA metabolites in rats following 6-OHDA lesions, and provides neuroprotection in MPTP models of PD, thus extending its beneficial effects.

Soy (Genistein)

The primary soybean is flavone genistein is a source of protein that appears to be neuroprotective in ovariectomized rats following 6-OHDA injection, thus suggesting it may be useful for the prevention of PD in post-menopausal women. In PD, genistein treatment resulted in dopaminergic neuron protection from lipopolysaccharide (LPS)-induced injury via inhibition of microglia activation. Genistein pretreatment improved spatial learning and memory in parkinsonian rats and restored tyrosine hydroxylase (TH), dopamine transporter (DAT) and Bcl-2 mRNA expression in the midbrain of MPTP-treated animals. Restored levels of DA and its metabolites, dihydroxyphenylacetic acid, and homovanillic acid, in the striatum were also observed after genistein administration. Additionally, genistein attenuated rotational behavior, protected SNpc neurons, and preserved motor function from 6-OHDA toxicities. Genistein's neuroprotective actions may regulate mitochondria-dependent apoptosis pathways and suppress ROS-induced NF-κB activation.

Vitamin D, C, and E

Vitamin D deficiency is prevalent in PD patients; yet, it is unclear if a reduction in vitamin D is a cause or consequence of PD. Vitamin D plays a role in regulating Ca^{2+} homeostasis and if disrupted, SNpc dopaminergic neuron loss is accelerated. This suggests that dietary regulation of vitamin D may be effective in protecting individuals from PD or slowing PD progression. In animal and cell culture models of PD, vitamin D supplementation was found to be beneficial in slowing disease progression. In human studies, however, high consumption of food containing vitamin D increased the risk of PD.

Meat

Meat is another source of animal fat and its consumption may be associated with the incidence of PD but the evidence from prospective studies is limited. Interestingly, intake of processed meat and sausages was inversely associated with PD risk in women. This finding is surprising given the higher incidence of mortality, cardiovascular diseases, and diabetes associated with processed meat consumption.

Conclusion

PD is more than a disease of the nigrostriatal dopaminergic system. The neurodegenerative process affects multiple central and peripheral systems. Currently, optimal symptomatic therapy for PD often consists of a cocktail of agents with diverse pharmacologic actions. This contrasts with usual practice in conditions such as epilepsy, for which monotherapy is the goal. Although dopaminergic therapy remains the mainstay, a wide variety of no dopaminergic agents are also used as highlighted throughout this review. On the other hand, many of these symptoms respond poorly or incompletely to available therapies, further emphasizing the urgency for greater research attention to these problems. The increasing recognition of extranigral aspects of PD will ultimately lead to earlier recognition of the onset of the disease and thus improve effectiveness and use of future neuroprotective therapies. In addition, more effective treatments for many of the disabling no motor symptoms and late-stage dopa-resistant motor symptoms will be possible with advances in our understanding of the pathogenesis of these features since nutrients affect mitochondrial energy function and provide vital antioxidant functions that ameliorate the free-radical byproducts of oxidative phosphorylation. A poor diet may lead to increased oxidative stress, which could impede the antioxidant defense system. In contrast, a well-balanced diet rich in a variety of foods, including numerous servings of vegetables and fruits and moderate amounts of omega-3 fatty acids, tea, caffeine, and wine may provide neuroprotection. After reviewing the literature, the medical community remains in suspense. Data speaks in favor of an interaction between levodopa treatment and the presence of *H. Pylori* in the upper GI tract. By eradication of *H. Pylori*, improved levodopa bioavailability and treatment efficacy is achievable. Whether or not obligatory screening and treatment of all patients with concurrent PD and *H. Pylori* should be pursued is a matter of

debate. In cases having poor symptomatic control and considerable motor fluctuations, measures aimed at *H. Pylori* diagnosis and eradication seem justified.

Conflict of Interest

The authors declare no conflicts of interest.

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