

Nutrition and Nonmotor Symptoms of Parkinson's Disease

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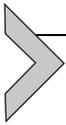
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Abstract

To date, no guidelines exist for the screening, evaluation, and management of nutritional status in PD. Dozens of studies demonstrate an association between diet in adulthood with subsequent risk of developing PD. Individuals with PD are at increased risk of malnutrition due to the increased metabolic demands and disease pathophysiology. Risk of malnutrition is further complicated by anosmia, swallowing difficulties, constipation, and drug–nutrient interactions. An emerging body of evidence suggests that the

intestinal tract is affected early in the disease, creating therapeutic opportunities for early intervention. Dietary modification and nutritional supplementation may improve symptoms of constipation, depression, insomnia, dystonia, and help prevent cognitive dysfunction. This review summarizes the state of the science related to nutrition and nonmotor symptoms of PD.



1. INTRODUCTION

Nutrition is the study of that which must be exogenously obtained for human health and survival. A nutrient is considered *essential* if it “serves an indispensable physiologic function, but cannot be synthesized endogenously at an adequate rate by healthy subjects” (Chipponi, Bleier, Santi, & Rudman, 1982). The determination of dietary essentiality had traditionally been established through classic feeding studies using purified diets with, or without, the nutrient being studied. Over time, if a nutrient is essential, a deficiency syndrome will emerge as signs and symptoms of impaired growth, function, biochemical alterations, or symptoms of illness become apparent.

Conditionally essential nutrients are those which are ordinarily synthesized in the body in sufficient amounts to meet physiological requirements, but must be exogenously supplied during periods when physiologic demands are greater than biosynthetic capacity. Unique nutritional requirements may additionally occur as a result of genetic polymorphisms, impaired absorption, or the presence of metabolic disease.

Thus far, a set of Parkinson’s specific nutritional recommendations has not been developed. The US Department of Agriculture (USDA) Food and Nutrition Information Center (FNIC) maintains an information database of Dietary Reference Intakes (DRIs) for vitamins, minerals, and macronutrients developed by the Institute of Medicine (IOM) of the National Academy of Science (NAS). The DRI levels have largely replaced the Recommended Daily Intake or Reference Daily Intake (RDI) system still used for product labeling. The RDI is the intake considered to be sufficient to meet the needs of 97.5% (2 standard deviations below the mean) of the healthy population.

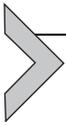
The quantification of the minimum required dose to prevent deficiency symptoms is determined by incremental refeeding until the dose resulting in syndrome resolution is reached (Chipponi et al., 1982).

In classic deprivation studies, the stages of deficiency are as follows:

Stage 1 Deficiency: Physiologic function continues normally while stores are being depleted. Adipose tissue, bone, muscle, storage forms, etc. act to maintain serum concentrations, e.g., depletion of calcium from bones.

Stage 2 Deficiency: The depletion of body stores results in biochemical alterations, although clinical symptoms are not yet apparent, e.g., elevated homocysteine in response to vitamin B12 or folic acid insufficiency.

Stage 3 Deficiency: In addition to biological perturbations, clinical symptoms become apparent, e.g., dementia and dermatitis as a result of niacin deficiency.



2. EVIDENCE FOR NUTRITIONAL DEFICIENCIES IN PD

2.1 Coenzyme Q10

Coenzyme Q10, or ubiquinone, is a fat-soluble coenzyme found primarily in the mitochondria of eukaryotic cells. It is an essential component of the electron transport chain, and thus the generation of ATP. In 2012, a case-controlled study of 22 patients with PD and 88 age- and gender-matched controls compared the frequency of nutritional deficiencies using a Functional Intracellular Assay (FIA). Thirty-four percent of individuals with PD were deficient in coenzyme Q10, compared to only 8.5% of controls ($P = 0.006$) (Mischley, Allen, & Bradley, 2012).

2.2 Glutathione

Glutathione is a tripeptide comprised of glycine, cysteine, and glutamic acid. Essential for life (Winkler et al., 2011), glutathione is both endogenously synthesized and fortified by diet. As the most abundant low molecular weight thiol, GSH plays critical roles as a reducing agent and in cellular detoxification (Forman, Zhang, & Rinna, 2009). “Parkinson’s Disease: A disorder due to nigral glutathione deficiency?” was published in 1982 following the discovery that postmortem glutathione concentrations were depleted in the substantia nigra of PD samples compared to age-matched controls (Perry, Godin, & Hansen, 1982). These findings were replicated in a follow-up study in which the authors concluded the most reasonable explanation for the glutathione deficiency is that a neurotoxic compound that can be conjugated with glutathione is accumulating in the substantia nigra (Perry & Yong, 1986). More recently, among 58 individuals with

idiopathic PD, the lower the whole blood glutathione concentration, the more severe their PD symptoms, as measured by the Unified PD Rating Scale (UPDRS) score ($P = 0.02$, 95% CI: -13.96 , -1.14) (Mischley et al., 2016).

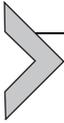
2.3 Lithium

Lithium is an essential mineral found in all cells of the human body. Lithium cannot be synthesized endogenously, and thus must be obtained through diet, fortification, or supplementation. It is found in trace amounts in soil, where it is unevenly distributed in the Earth's crust. The majority of lithium comes from the consumption of water, vegetables, and grains, with the average consumption in the United States estimated to range between 650 and 3100 $\mu\text{g}/\text{day}$ (Schrauzer, 2002). Low lithium concentrations in the drinking water have been associated with depression in several studies (Giotakos, Nisianakis, Tsouvelas, & Giakalou, 2013; Schopfer & Schrauzer, 2011). In the CNS, lithium is instrumental in maintaining homeostasis of the second messenger cAMP (Montezinho et al., 2004) and plays a role in the regulation of autophagy (Yao, Zhao, Khan, & Yang, 2013), which has been shown to be dysregulated in neurodegenerative disease (Rosello, Warnes, & Meier, 2012). In a rodent model, lithium enhances the clearance of intracellular α -synuclein (Motoi, Shimada, Ishiguro, & Hattori, 2014). A clinical case series of lithium status in 80 patients with PD found 63.8% of samples were deficient in lithium, defined as greater than 2 standard deviations below the laboratory reference range (Mischley, 2013).

2.4 Thiamine

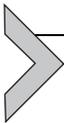
Thiamine, or vitamin B1, is an essential cofactor for several key enzymes required for brain oxidative metabolism. Thiamine is naturally found in high concentrations in the human substantia nigra (Baker et al., 1984). In thiamine deficiency, there are reduced levels of striatal dopamine, and intrastriatal administration of thiamine has been shown to enhance the release of dopamine (Yamashita, Zhang, & Nakamura, 1993). In 24 PD patients and 40 matched controls, PD patients had lower concentrations of free thiamine in the cerebrospinal fluid, and this depletion was not seen in individuals taking levodopa (Jimenez-Jimenez et al., 1999). Recently, an open-label pilot study of 100 mg intramuscular thiamine twice weekly in 50 patients with PD reported significant improvement in motor and

nonmotor symptoms, which was sustained during the 3–27-month follow-up period (Costantini & Fancellu, 2016; Costantini et al., 2015).



3. PD INCREASES RISK OF MALNUTRITION

A systematic review of the literature based on available longitudinal data revealed that having PD is a significant risk factor for malnutrition (OR: 2.450; $P = 0.047$), as were increased age, constipation, poor-to-moderate self-reported health status, cognitive decline, dementia, apathy, dysphagia, and institutionalization, all of which are commonly seen in PD (Moreira et al., 2016). Using the Mini Nutritional Assessment (MNA), a validated screening tool for nutritional status, the prevalence of malnutrition in patients with PD ranges from 15% to 22% (Wang et al., 2010).

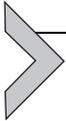


4. DIET AND RISK OF PD INCIDENCE

Several prospective longitudinal studies have been conducted in which diet and nutrition have been periodically assessed throughout adulthood and incidence of PD documented within the cohort. Collectively, these data are consistent in suggesting vegetables, fruits, nuts, seeds, and fish contain phytochemicals and other constituents with neuroprotective potential (Gao, Cassidy, Schwarzschild, Rimm, & Ascherio, 2012; Gao et al., 2007; Jiang, Ju, Jiang, & Zhang, 2014; Qi & Li, 2014). On a molecular level, a decreased risk of PD has been associated with increased flavonoid, carotenoid, and nicotine content of the diet (Alcalay et al., 2012; Gao et al., 2012; Miyake et al., 2011; Nielsen, Franklin, Longstreth, Swanson, & Checkoway, 2013).

Dairy consumption has been associated with an increased risk of PD in four of five prospective observational studies to explore the role of diet and risk of PD incidence (Chen et al., 2007; Chen, Zhang, Hernan, Willett, & Ascherio, 2002; Kyroziis et al., 2013; Park et al., 2005). The association was not observed in the Japanese cohort (Miyake et al., 2011). Some studies suggest the association is stronger in men and greatest with cream and ice cream. Hypotheses for the association include dairy's ability to lower uric acid levels (Zgaga et al., 2012) or the presence of a neurotoxicant in dairy products, such as organochlorine pesticide residues (Fitzmaurice, Rhodes, Cockburn, Ritz, & Bronstein, 2014). Lactose deficiency, the inability to digest the milk sugar lactase, is increasingly common with age. Not only does continued consumption of lactase lead to intestinal inflammation

and symptoms of gas, bloating, constipation, and/or diarrhea, in one study up to 90% of lactose-deficient individuals had evidence of small intestinal bacterial overgrowth (SIBO) (Almeida et al., 2008), a condition found in over 50% individuals with PD and fewer than 10% of controls (Gabrielli et al., 2011).



5. AN INTESTINAL DISEASE THAT SPREADS TO THE BRAIN?

The gastrointestinal tract is affected early in the course of PD. Lack of thirst, dehydration, constipation, impaired olfaction, and irritable bowel syndrome have been documented decades prior to the onset of motor symptoms (Lai, Liao, Lin, & Sung, 2014). On a cellular level, the earliest signs of pathology occur in the intestinal track, with α -synuclein aggregations in the salivary glands and intestinal mucosa at least a decade prior to the onset of PD motor symptoms (Adams-Carr et al., 2016; Mukherjee, Biswas, & Das, 2016). There is an emerging body of literature suggesting the pathology of PD may spread from the gut to the brain via the vagus nerve; a large Danish epidemiological study demonstrated that individuals who have had their entire vagus nerve severed (as a treatment for peptic ulcer) had an almost 50% reduction in PD (Svensson et al., 2015).

5.1 Digestive Enzyme Insufficiency

While attention has turned to the vagus nerve as a potential channel for propagation of disease, little attention has been given to the role of the vagus nerve in maintaining gastrointestinal health. In response to smell, taste, chewing, and anticipation of food, the vagus nerve stimulates the release of hydrochloric acid (HCl) from gastric parietal cells. Hypochlorhydria/achlorhydria is the reduction/absence, respectively, of HCl in the gastric mucosa. Achlorhydria can result in impairment of absorption of vitamin B12 (Holt, 2007), folic acid (MacKenzie & Russell, 1976), and is associated with SIBO (Husebye, Skar, Hoverstad, & Melby, 1992; Pereira, Gainsborough, & Dowling, 1998). Among patients who had become refractory to levodopa therapy, 22/38 patients (58%) were found to have reduced gastric acid. Following 2 weeks of coadministration of 30 mL of lemon juice, an attempt at acidifying the stomach to increase medication availability, with each dose of levodopa, there was a measurable increase in circulating L-dopa concentration after 60 and 180 min, with corresponding improvements in

rigidity, akinesia, and gait. Although rarely discussed, this finding supports the hypothesis that hypochlorhydria is prevalent and relevant in PD and should be considered in those with erratic medication responsiveness.

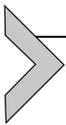
HCl production can be measured via a variety of techniques including gastric acid aspiration tests, Heidelberg testing (pH sensor on a swallowed capsule), and via endoscopy (Ghosh, Lewis, Axon, & Everett, 2011). Pancreatic insufficiency can be evaluated using fecal elastase testing. In a PD patient with suspected hypochlorhydria, enzymatic supplementation (HCl, betaine, pepsin) resolved lower abdominal pain in a published case report. Upon discontinuation of the enzyme supplement, the abdominal pain returned, and was again relieved when the enzyme supplement was restarted (Kines & Krupczak, 2016).

5.2 Celiac Disease

Celiac disease is an autoimmune disease in which the ingestion of the dietary protein gluten leads to damage of the small intestine. Celiac disease may present at any age. Interestingly, it is not uncommon for patients with celiac disease to have no gastrointestinal symptoms, while neurological symptoms are common. In celiac patients with neurological disorders, there is a high prevalence of antineuronal antibodies (Hadjivassiliou et al., 2010). A 2014 case report of a 75-year-old male without gastrointestinal symptoms presented with a 1-year history of gait disorder, instability, and fatigue, with hypomimia, bradykinesia, rigidity, and postural instability on physical examination. Single-photon emission computed tomography (SPECT) DaT-SCAN showed a pronounced decrease of left putamen radiotracer uptake and moderate decrease in the contralateral putamen. Clinical and SPECT data led to a diagnosis of PD. Evidence of malabsorption led to the evaluation for celiac disease, for which the patient was positive (anti-gliadin ab IgA, IgG, anti-TTG, + antiendomysial antibodies). Following the gastroenterologist-prescribed gluten-free diet, the patient had clinically verified “almost complete remission of symptoms” through the 18 months of follow-up, while SPECT evidence showed continued evidence of degeneration (Di Lazzaro, Capone, Cammarota, Di Giuda, & Ranieri, 2014). Celiac disease should be suspected in any individual with unexplained evidence of malabsorption, low serum iron or folic acid, anemia, or osteoporosis (Holt, 2007). The diagnosis is made if elevated titers of antitissue transglutaminase or antiendomysial antibodies are identified.

5.3 *Helicobacter pylori*

Almost one-third of individuals with PD are infected with *Helicobacter pylori*, a common infection in the human upper digestive tract. Infected individuals do not report gastrointestinal symptoms more than uninfected individuals, although they tend to be older and have worse motor scores (Tan et al., 2015). When the serum of 30 *H. pylori* positive and 30 negative PD patients was compared, researchers identified the presence of 13 autoantibodies against proteins essential for neurological function in the group with *H. pylori* (Suwarnalata et al., 2016). Because *H. pylori* affects levodopa absorption and infection may aggravate the degenerative course of PD, eradication is essential. A study of 27 individuals with PD and *H. pylori* infection demonstrated statistically significant improvements in levodopa onset time, overall ON duration, UPDRS scores, and PDQ-39, a quality-of-life measure, 12 weeks following eradication (Hashim et al., 2014). *H. pylori* screening should be performed on patients with gas, bloating, nausea, loss of appetite, belching, gnawing or burning abdominal pain, or bad breath.



6. SYMPTOM-SPECIFIC NUTRITIONAL CONSIDERATIONS

6.1 Constipation

Constipation has been shown to affect approximately 85% of individuals with PD and increases the risk of malnutrition (Maeda et al., 2017; Wang et al., 2010). In some cases, lack of thirst and constipation have been shown to precede motor symptoms by more than 18 years (Ueki & Otsuka, 2004). In addition to physical discomfort, constipation decreases appetite, interferes with the uptake of medications, leads to the reabsorption of toxicants, and is associated with growth of abnormal intestinal microflora, a condition known as dysbiosis, which can further perpetuate delayed gastric emptying. In a study of 51 drug-naïve individuals with PD and 20 health age-mated controls, serum 25-hydroxyvitamin D3 concentrations were decreased in the group with delayed gastric emptying time. The authors concluded vitamin D insufficiency may be implicated in the pathogenesis of delayed gastric emptying in PD (Kwon et al., 2016).

Probiotic supplements have been shown to improve symptoms of bloat, pain, and improved stool consistency in patients with PD. Use of a *Lactobacillus casei* Shirota supplement in 40 constipated PD patients for 5 weeks resulted in an increase in number of days per week with normal consistency stools ($P < 0.01$), reduction in number of days participants felt bloated

($P < 0.01$), reduction in abdominal pain ($P < 0.01$), and reduction in sensation of incomplete emptying ($P < 0.01$) (Cassani et al., 2011). Another study looked at the effectiveness of a fermented milk containing probiotics and prebiotics in PD patients with Rome III-confirmed constipation. The results of the randomized, double-blind, placebo-controlled trial demonstrated the probiotic/prebiotic supplement increased the number of complete bowel movements per week ($P = 0.002$), the primary endpoint (Barichella et al., 2016).

6.2 Cognitive Impairment

Abdominal obesity and impaired olfaction at diagnosis were associated with reduced Mini-Mental Status Examination 3 years following PD diagnosis (Vikdahl, Domellof, Forsgren, & Haglin, 2015). Not specific to PD, a recent meta-analysis of 21 cohort studies investigated associations between fish and polyunsaturated fatty acid intake and risk of cognitive impairment. Among the 181,580 participants with 4438 follow-up periods ranging from 2.1 to 21 years, dietary fish was associated with lower risk of cognitive impairment and dementia (Zhang, Chen, Qiu, et al., 2016). Individuals should be encouraged to consume several servings of nonfried fish per week and DHA supplementation should be considered.

Homocysteine, a normal product of human metabolism, is neurotoxic at high concentrations, accelerating dopaminergic degeneration, and is an established risk factor for developing cognitive impairment in PD (Xie, Feng, Peng, Xiao, & Zhang, 2017). Increase in homocysteine can be due to deficiency of vitamins B12, B6, folic acid, or betaine (trimethylglycine). It is well established that levodopa interferes with folic acid uptake and utilization, and there is a dose-response relationship between levodopa use and homocysteine concentrations (Paul & Borah, 2016). Individuals on levodopa or with symptoms of cognitive decline should have homocysteine concentrations measured annually; individuals with concentrations greater than $10 \mu\text{mol/L}$ should be prescribed a homocysteine-lowering supplement.

6.3 Depression and Anxiety

Individuals with PD and compromised nutritional status are more likely to be affected by mood disorders, such as anxiety and depression (Fereshtehnejad et al., 2014). A clinical case series of 117 consecutive Chinese patients found that Geriatric Depression Scale score was the second

most important predictor of nutritional impairment, following constipation (OR, 1.166; 95% CI, 1.042–1.304; $P = 0.007$) (Wang et al., 2010). A 2008 pilot study of 31 individuals with PD and depression was randomized to receive omega-3 fish oil or mineral oil capsules for 12 weeks; whether or not they were taking antidepressants, individuals randomized to receive the omega-3 fish oil capsules showed a significant decrease in symptoms of depression, as measured by the Montgomery-Asberg Rating Scale (MADRS) and the Clinical Global Impression Scale (CGI) (da Silva et al., 2008).

Anxiety disorders are common in PD, occurring in approximately a quarter of patients (Dissanayaka et al., 2010). There is even evidence that having anxiety increases an individuals' risk of developing PD. The extent to which anxiety may be an early PD symptom or share an underlying pathophysiology with PD is yet to be determined (Weisskopf, Chen, Schwarzschild, Kawachi, & Ascherio, 2003). Poor nutritional status, as measured by the MNA, is inversely correlated with serum cortisol (Haglin & Backman, 2016). There is an emerging body of literature elucidating the relationship between diet and mood, likely mediated by the intestinal microbiota. There is evidence that vegans report less stress and anxiety than omnivores (Beezhold, Radnitz, Rinne, & DiMatteo, 2015). Taken together, these data suggest a plant-based diet, including fish, and possibly an omega-3 fatty acid supplement, should be prescribed to PD patients with anxiety or depression.

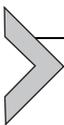
6.4 Sleep Disorders

While most humans can synthesize sufficient amounts of melatonin to meet physiological needs, there is evidence that individuals with PD inadequately produce this hormone (De Pablo-Fernandez et al., 2017). Thus, like dopamine, it may be exogenously required, or a conditionally essential nutrient. As already discussed, there is a substantial body of literature suggesting glutathione production is inadequate in PD. Because of the interdependent circadian rhythms of glutathione and melatonin, insufficient glutathione synthesis during the day will interfere with melatonin production at night, and vice versa (Pablos et al., 1998). In an uncontrolled trial of 30 individuals with PD, 3 mg of melatonin was associated with a 21% decrease on Parkinson Fatigue Scale ($P < 0.05$), improvements in sleep (PD Sleep Scale) ($P < 0.05$), decrease in state anxiety (Spielberger's scale) ($P < 0.05$), and improvement in quality of life (PDQ-39) ($P < 0.05$)

(Datieva, Rosinskaia, & Levin, 2013). While there was no change in polysomnography, individuals with PD randomized to receive 3 mg melatonin reported improved quality of sleep ($P = 0.03$) over placebo after 4 weeks of supplementation (Medeiros et al., 2007). A meta-analysis of nine randomized controlled trials suggests exogenous melatonin is effective for improving overall sleep quality and the clinical and neurophysiological aspects of rapid eye movement sleep behavior disorder in PD (Zhang, Chen, Su, et al., 2016).

6.5 Dystonia

A study seeking to evaluate whether lithium might be an effective treatment for dyskinesia found that, while not effective for dyskinesia, there was an unexpected improvement in dystonia, a state of sustained muscle contraction common in PD, in four of the study participants. The authors stated, “three patients on levodopa reported relief of muscular cramps and painful toe curling only when taking lithium carbonate ... another reported a welcome reduction in oculogyric crises” (McCaul & Stern, 1974). Following the report that lithium carbonate was capable of reducing dystonia, seven patients with disabling dystonia were recruited for a double-blind, placebo-controlled study of 600 mg slow-release lithium carbonate, administered at bedtime. The study was designed to include three phases: the first phase was an open-label trial lasting at least 3 months. During phases 2 and 3, individuals were randomized to receive either lithium or placebo in a cross-over fashion, with both phases 2 and 3 designed to last for 2 months, followed by phase 4, an open-label portion of the study. The authors reported, “Painful dystonic cramps were much reduced or abolished in 19 of 21 treatment periods with lithium (13 open, 6 blind). They returned to (6) or toward (1) pretreatment severity in all 7 placebo periods. The beneficial effect appeared 1–16 days after starting and disappeared 1–14 days after stopping lithium” (Quinn & Marsden, 1986).



7. DRUG–NUTRIENT INTERACTIONS

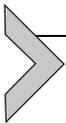
7.1 Levodopa

Dietary protein interferes with levodopa uptake and patients should be advised to take levodopa on an empty stomach, or with a small meal low in protein (Robertson et al., 1991). Constipation also interferes with uptake of levodopa, a major determinant of medication effectiveness. If constipated,

individuals with erratic response to levodopa focus improving bowel transit time; suggestions include a plant-based diet, increased fluid intake, and vitamin D (Kwon et al., 2016) and probiotic supplementation (Barichella et al., 2016; Cassani et al., 2011) should be considered. As previously discussed, a highly acidic gastric environment is required for activation of levodopa, and individuals with PD are at increased risk of HCl insufficiency; other symptoms of malabsorption, e.g., weight loss and osteopenia, should warrant an evaluation of HCl adequacy.

Not all drug–nutrient interactions are negative, as several studies suggest CDP-choline has a levodopa-sparing effect (Cubells & Hernando, 1988). 500–1200 mg of CDP-choline has been shown to permit a 30%–50% reduction in levodopa dose, respectively (Cubells & Hernando, 1988; Eberhardt, Birbamer, Gerstenbrand, Rainer, & Traegner, 1990), which has been attributed to an increase in pre- and postsynaptic dopamine receptors and an increase in the synthesis of tyrosine hydroxylase (Marti Masso & Urtasun, 1991). For individuals suffering from levodopa-induced dyskinesia (LID), high-dose omega-3 DHA (approximately 5 g) was associated with a 30%–50% reduction in LID in a primate model of LID and a clinical case series (Mischley & McNames, 2013; Samadi et al., 2006).

Perhaps most importantly, levodopa interferes with the uptake and metabolism of folic acid, as discussed in Section 6.2. Given the high risk of dementia in PD and the lack of effective treatments, prevention strategies should include utilization of levodopa-sparing therapies, e.g., CDP-choline, and annual homocysteine screening.



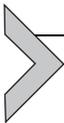
8. ASSESSMENT OF NUTRITIONAL STATUS

Evaluation of nutritional status should always begin with a dietary history. Providers should be trained to ask about diet, specifically looking for high-calorie foods low in nutritional content (e.g., fried foods, sugar-sweetened beverages) as a risk factor for malnutrition. The majority of the patient's diet should be comprised of fresh fruits, vegetables, nuts and seeds, whole grains, beans, and nonfried fish.

Physical exam is an essential component of nutritional evaluation. While reduced body mass index is well known to be associated with malnutrition, obesity, too, is associated with malnutrition and adipose tissue is a major source of inflammatory cytokines (Gulland, 2016). As there is no comprehensive way to screen for nutritional adequacy, clinicians must look for signs and symptoms associated with the nutrients in questions. For example, when

mineral deficiencies are suspected, such a calcium or magnesium insufficiency, tapping on the facial nerve can result in a positive Chvostek sign, in which the facial muscles on the ipsilateral side of the face will twitch.

The same is true for laboratory assessments of nutritional status; there is no single test, or even panel of tests, one can order to determine nutritional adequacy. Providers must understand the nutrient's physiological role(s) to order the correct tests; for example, neurological and/or psychological abnormalities associated with vitamin B12 deficiency can occur in spite of normal serum B12 concentrations (Andres et al., 2005; Lindenbaum, Rosenberg, Wilson, Stabler, & Allen, 1994). Thus, a comprehensive screening for vitamin B12 status includes serum cobalamin, methylmalonic acid, homocysteine, and mean cell volume (Wong, 2015). Blood is not the only biospecimen used for nutritional assessment, either. For example, the gold standard for assessing lithium status is hair (Anke, Arnhold, Groppe, & Krause, 1991), urine for iodine (Markou et al., 2002), and breath tests for the detection of SIBO (Rezaie et al., 2017). While reference ranges do not yet exist, stool tests are commercially available that use polymerase chain reaction methodology to provide insight into the patient's intestinal microbiome. As more research becomes available on the association between dysbiosis and PD, stool tests are likely to grow in popularity.



9. CONCLUSIONS

Two-hundred years after the original description of PD, attention is finally turning to the potential roles of diet and nutrition in disease etiology and progression. At first glance, it is difficult to imagine such a complex, debilitating syndrome could be notably influenced by something as inexpensive and simple as a food or supplement. Those individuals hesitant to entertain the possibility are reminded that 3 million people died of scurvy before it was discovered that the disease could be cured with limes. Especially poignant is the fact that scurvy was successfully treated with limes for 200 years *before* the ascorbic acid molecule was discovered. Nutritional interventions have been so successful at curing disease that clinicians take the need for nutritional evaluation for granted, and many would have a hard time recognizing pellagra if a patient presented with it. This 200th year anniversary of PD is likely to herald enhancements in diagnostic and treatment modalities, as well as foster emerging paradigms, including the development of nutritional guidelines for the screening, evaluation, and management of PD.

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