

Ensuring good nutritional status in patients with Parkinson's disease: challenges and solutions

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Abstract: Nutrition is becoming an important tool in the management of the main chronic diseases, including Parkinson's disease (PD). Nutritional status has been shown to deteriorate with the progression of PD, due to motor and nonmotor complications. Dietary protein can reduce the effectiveness of levodopa treatment in PD patients, since the large neutral amino acids and levodopa share the same saturated carrier system, while fiber can improve the drug bioavailability. Moreover, nutrition seems to be directly involved in PD risk: high dietary intakes of animal fat, iron, mercury, and dairy, as well as western dietary patterns can increase it, while intake of some antioxidant compounds and plant-based dietary patterns can be protective. The means of ensuring good nutritional status in PD range from providing adequate energy and nutrients for the body, to considering in a broader perspective, the management of motor and nonmotor symptoms and chronic levodopa treatment complications, as well as pursuing potential neuroprotection. This review summarizes the most relevant results in the literature, and discusses the contribution of diet in the management of PD.

Keywords: levodopa, Mediterranean diet, plant-based diet, protein-redistribution diet, vegetarian diet

Introduction

Nutrition is becoming an important tool in the management of some of the main chronic diseases, not only from the point of view of bodily nutritional requirements. Food can provide protective as well as harmful factors, which can act over time with cumulative, synergic, or antagonistic effects, influencing not only the onset of a disease, but the rate of progression as well. The role of food, namely dietary protein, in levodopa-treated Parkinson's disease (PD) patients was first described as far back as 1975,¹ but even if many authors feel that nutrition should become a part of the therapeutic strategy in PD management, this issue is still poorly addressed by current research. To date, few intervention studies have been performed, while information on hazardous and protective dietary factors comes mainly from nutritional epidemiology. Although single and multiple genetic factors are involved in PD pathogenesis,²⁻⁵ research suggests that the disease can represent the final pathway of a combination of genetic and environmental factors.⁶⁻⁸ Dietary factors can alter the oxidative balance in the brain, and provide both environmental neurotoxins and neuroprotection. Although PD occurs worldwide, its prevalence is two- to five-times higher in industrialized countries than in developing countries,⁹ and is higher in US migrant groups than in subjects of the same ethnicities living in their country of origin.¹⁰ The lowest prevalence ratios have been reported in People's Republic of China, Japan, and Africa,¹¹ countries where plant foods are

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staples in the diet, suggesting that they may contain protective compounds.¹² In PD, body weight gain and loss can also occur, and both changes in energy expenditure and food intake may contribute. Moreover, food is involved in the pharmacokinetics of the gold standard of treatment: levodopa.

Thus, ensuring a good nutritional status in PD ranges from providing adequate energy and nutrients for the body, to considering, in a broader perspective, the management of motor and nonmotor symptoms and chronic levodopa treatment complications, as well as pursuing potential neuroprotection.

Nutritional status in PD

PD patients have been found to be at risk for weight changes and malnutrition. Inadequate intake of energy and nutrients cause weight loss and malnutrition, which in turn may worsen the neurological status, and is associated with many adverse outcomes related to health and quality of life.^{13–15} Most studies on PD patients reported weight loss, which correlated with disease progression and motor disabilities, but also with the age at diagnosis and the presence of psychiatric symptoms.¹⁶ One meta-analysis concluded that PD patients had a significantly lower body mass index (BMI) than controls, with the lowest BMIs in the most advanced stages.¹⁷ A systematic review reported a malnutrition prevalence range of 0%–24%, while 3%–60% of PD patients were found to be at risk.¹⁸ During a 3-year follow-up period, the percentage of PD patients at risk of malnutrition increased from 22.9% to 34.3%.¹⁹ Loss of appetite, constipation, early satiety, and swallowing problems were the more frequent symptoms influencing food intake; older age at diagnosis, living alone, higher neurologic and depression scores, and higher levodopa-equivalent-daily-dose/body weight (mg/kg) ratio predicted malnutrition.^{20,21} The lighter PD patients received greater cumulative dosages of levodopa/kg,²² and BMI correlated negatively with the daily levodopa dosage/kg and total dopaminergic dosage/kg.²³ Dyskinetic patients, whose body weight decreased during the course of the disease, received higher total levodopa daily dose, and higher levodopa/kg daily dose. Weight loss and levodopa/kg daily dose turned out to be the only significant factors for dyskinesia,²⁴ suggesting the existence of a downward spiral linking body weight, levodopa dosage, and dyskinesia.

Weight loss and malnutrition seem to be multifactorial events in PD: some of the motor symptoms associated with the disease (ie, involuntary movements like tremors and dyskinesia) can increase energy expenditure, while other disease symptoms and medication side effects can limit

food intake. Finally, PD-related psychosocial and cognitive limitations can increase susceptibility to malnutrition.

While levodopa correlates with weight loss, other dopaminergic agents can cause weight gain,²⁵ and increase the risk of compulsive behavior, including compulsive eating.^{26,27} Weight gain was also reported in patients that underwent deep brain stimulation:^{15,28,29} it correlated inversely with the preoperative weight; was more pronounced in bilateral than unilateral pallidal or subthalamic nucleus surgery;²⁹ and was linked to a significant decrease of resting energy expenditure, lipid oxidation, and protein oxidation.³⁰

The increase in body weight is also multifactorial, and results from dysregulation of the energy requirement–input balance. It involves not only changes in energy expenditure due to motor improvement/attenuation of involuntary movements, but also the alteration of hypothalamic regulation, and the influence on eating behavior modulated by dopamine and dopaminergic treatment through a direct dopamine-agonist effect on limbic D3 receptors involved in the control of feeding.^{25,28,31} Weight gain despite unaltered eating may be the consequence of reduced energy expenditure. Disruption of homeostatic control results in increased appetite, and compulsive eating behavior may also occur. Hyperdopaminergic eating behavior is characterized by compulsive and nocturnal eating; conversely, hyperphagia in the hypodopaminergic state is part of the synonymous behavior, accompanied by apathy and characterized by random snacking and emotional eating.³²

Food and pharmacological treatment

PD is related to the reduction of brain dopamine content. The amino acid levodopa is the direct biochemical precursor of dopamine, and it is the powerful pharmacological treatment that restores adequate dopamine activity.³³ Unlike dopamine, levodopa can enter the brain, where it is eventually decarboxylated to dopamine. In the early stages of PD, levodopa is highly effective, but with the progression of the disease its delivery to the brain fluctuates, and conversely affects the neurological status.³⁴ PD advanced stages are complicated by motor fluctuations, the “on–off” phenomenon, alternating “off” periods (motor blocks) with “on” periods of normal movements or dyskinesia. Food affects levodopa effectiveness in many ways. As a consequence of multiple interferences, levodopa intestinal absorption can become erratic and cause instability of its plasma concentration, while dissociation between levodopa plasma concentration and its clinical effect may be caused by dietary protein. Gastric mucosa contains

the enzyme aromatic amino acid decarboxylase, so the gastric accumulation of levodopa can reduce its bioavailability. Gastric pH and meal characteristics (high energy content of food and meal size) reduce gastric emptying rate.³⁴ A diet rich in soluble fiber can slow gastric emptying rate, unlike a diet rich in insoluble fiber,³⁵ which can even increase levodopa bioavailability.³⁶ Finally, even dietary protein can affect levodopa bioavailability.^{37,38} Proteins are biological molecules formed by chains of smaller units, the amino acids; they represent, together with carbohydrates and lipids, the dietary macronutrients, because they provide energy. Protein functions are moreover not primarily energetic, as they contribute to the structure of the tissues and perform regulatory, catalytic, and transport actions. As levodopa belongs to the class of large neutral amino acids (LNAA), its entry into the bloodstream and through the blood–brain barrier (BBB) depends on the active saturable carrier system: the LNAA transporter. So, at both levels, levodopa competes for the carrier with the other dietary LNAA (tyrosine [the precursor of levodopa], phenylalanine, leucine, isoleucine, valine, tryptophan, and methionine) to cross gut mucosa and the BBB. As the equilibrium constant for LNAA active transport across the BBB is about ten-times less than for other tissues, and approaches the sum of postprandial LNAA concentrations, the critical site of interference for levodopa transport is at the BBB.³⁹ In 1975, the beneficial effect in fluctuating PD patients of a low-protein diet (10 g/day) on neurological status, and on total levodopa requirements, was first reported.¹ Since then, analogous clinical trials confirmed the benefit of dietary protein restriction and the influence of dietary protein on levodopa effectiveness, which correlated with plasma LNAA levels (with variability among studies),^{40–45} but not with blood levodopa levels.^{43–48} Accordingly, in patients with moderate to severe symptoms, some authors described higher protein intakes (1.27 versus 1.07 g/kg), which correlated with higher daily levodopa dosages.⁴⁹ In one study, the administration of a balanced carbohydrate:protein (5:1) mixture was also effective.⁵⁰ To avoid the risk of nutritional deficits, as far back as 1988, the “protein redistribution diet” (PRD) was proposed, in which protein intake, while not restricted, is concentrated in the evening meal, thus limiting protein interference in the daytime. PRD was effective in the long-term, giving significant reduction of diurnal motor fluctuations,^{51–53} although some authors reported that this benefit was limited to postprandial dose failures.⁵⁴ A 48-month successful follow-up, with 70% still-compliant patients, was reported,⁵⁵ while other authors had about 40% noncompliant patients after a 3-month period.⁵⁶ PRD acceptability seemed to progressively decrease over

time.⁵⁷ Current PD guidelines recommend protein intake manipulation for levodopa-treated fluctuating patients.⁵⁸ This intervention is effective in patients who had previously benefited from levodopa therapy, and its positive effect can already be seen within a week.⁵⁹ Benefit appears to be higher when the dietary intervention is applied in the early stages of PD.⁵⁷ Timing of levodopa doses in relation to mealtime is also important: the drug should be introduced no less than 30 minutes before meals, in order to reach the small-intestine quickly and unaltered, and to avoid erratic absorption due to the various effects of food.³⁴

Neuroprotection in PD

Growing evidence suggests that environmental and lifestyle habits, including nutrition, can play protective or detrimental roles in PD. Various food components can elicit neuroprotection, or trigger or exacerbate neurodegeneration, possibly also serving as a vehicle for environmental neurotoxins.^{60–62} Therefore, identifying dietary and lifestyle variables associated with PD may offer pathogenetic clues, and therapeutic and prevention opportunities.

Research supports the role of oxidative stress and lipid peroxidation in PD, which can also promote alpha-synuclein aggregation, a well-recognized event in the pathogenesis of the disease.^{63,64} Hence, it can be supposed that antioxidant molecules (ie, vitamins E and C, carotenoids, and other phytochemicals) can potentially play a protective role by neutralizing free radicals and preventing neuronal injury in the substantia nigra.⁶⁵ Among all dietary antioxidants, only vitamin E consumption has consistently proven to be protective: higher intakes were shown to reduce PD risk in population studies and in one meta-analysis.^{66–69} Only vitamin E intake from food was effective, not intake through supplements.⁶⁹ Vitamin E was also able to suppress signaling events responsible for microglial activation in cell cultures, suggesting further neuroprotective properties *in vivo*.⁷⁰ Vitamin C is highly concentrated in the central nervous system (CNS) and is primarily associated with the activity of glutamatergic neurons.⁷¹ Although it slowed the progression of the disease in association with vitamin E in a small pilot trial,⁷² research on this nutrient is still giving conflicting results.^{65–67,69} Carotenoids, the plant-form of vitamin A, also provide antioxidant effects; nevertheless, their serum levels and dietary intakes were shown to be unrelated to PD risk,^{66,67,69,73} although a Japanese study showed a protective effect for higher consumption of dietary beta carotene and vitamin E.⁶⁸ Finally, hyperhomocysteinemia, as well as folate deficiency, can increase neuronal vulnerability to oxidative

attacks, by decreasing glutathione peroxidase activity and reducing tissue stores of antioxidant vitamins.⁷⁴ So, it was suggested that higher dietary intakes of folate, vitamin B12, and vitamin B6 (cofactors in homocysteine metabolism) could reduce PD risk by decreasing plasma homocysteine levels. Nevertheless, no consistent relation was found with B12 and folate intakes: only vitamin B6 intakes were shown to exert protective effects in most studies.^{75–77} It is also worth mentioning that vitamin B6 can boost dopamine synthesis.⁷⁶ An almost doubled prevalence of vitamin D deficiency in PD patients was recently reported, and low plasma levels correlated with more advanced neurological status.⁷⁸ Vitamin D benefit in PD ranges from bone health to neuroprotection,⁷⁹ however, its adequacy is not dependent on diet, but on sunshine exposure and/or supplementation. For this reason, as we'll see later, nutritional recommendations in PD patients are the same as for the general population. Mercury, a heavy metal that can harm basal ganglia, has been recognized as a risk factor for many years now.⁸⁰ Even iron has been directly related to PD risk,^{81–83} through neurotoxicity from various possible mechanisms: intracellular iron concentration, hydroxyl radical production, and mitochondrial damage.⁸⁴

Studies which evaluated macronutrient intakes have produced inconclusive results: some authors reported that high animal fat intakes increased PD risk,^{81,85,86} while others found no correlation.^{83,87,88} Although the potential mechanisms remain speculative, it is assumed that animal fats (mainly saturated) can induce adverse changes in cell membrane lipid composition via oxidative stress.⁸⁹ They can also interfere with the endogenous metabolism of polyunsaturated fatty acids which, like vegetable fats, seem to be protective or neutral with regards to PD, although few studies are found on this subject.^{81,86,90–92}

Juglone, contained in walnuts, has been recently shown to protect brain cells in preclinical studies.⁹³ Juglone is an inhibitor of the enzyme Pin1, a major peptidyl-prolyl isomerase, which was found to be present in PD Lewy bodies (markers of the disease, consisting of cytoplasmic inclusions containing aggregates of α -synuclein) and to promote the formation of α -synuclein inclusions in cellular models.⁹⁴ It was also found that its activity is highly upregulated in cell cultures of PD brains,⁹³ suggesting a pathophysiological role of this enzyme in the dopaminergic pathway degeneration, and hence suggesting that walnut intakes can be beneficial for neuroprotection, not only as a source of polyunsaturated fatty acids.

Research focusing on single foods or food groups has shown that dairy product consumption, especially milk, can

increase PD risk,^{95–97} and can possibly introduce dopaminergic neurotoxins, such as pesticides and polychlorinated biphenyls.^{61,98} Meat consumption has also been linked to increased PD risk.⁸⁵ Meat, particularly red meat, besides the animal fat it contains, is the unique dietary source of heme iron, the bioavailability of which is high and cannot be downregulated. As previously described, iron can cause CNS damage.⁸⁴ Fish consumption can contribute to a high level of the body's mercury burden, thus increasing PD risk.⁸⁰ Although mercury contamination has usually been associated with saltwater fish, research found that even freshwater fish can contain mercury, due to human activities or to natural causes.^{99–103} The United States Environmental Protection Agency published in 2009 the results of a national study on freshwater fish, reporting that 48.8% of the sampled population of lakes had mercury tissue concentrations that exceeded the 300 ppb (0.3 ppm) human health Screening Values (SV) for mercury.¹⁰⁴

While research studies on the role of food in PD are lacking, the effect of a nonessential beverage, namely coffee, has been extensively investigated. As its consumption has been related to a lower PD risk,^{105–109} a protective role of caffeine against dopaminergic degeneration has been suggested. This benefit was found to be fairly strong among men and postmenopausal women not receiving hormone therapy. A negative estrogen–caffeine interaction has been hypothesized.^{105,107,110–112} The protective effect of drinking tea on PD risk was also widely explored, and a recent meta-analysis reported a beneficial, apparently, non-dose-dependent, effect.¹¹³ Other studies suggested that beneficial effects of tea could be due to its content of polyphenolic compounds, ie, theaflavin in black tea and (–)-epigallocatechin-3-gallate in green tea.^{61,114} Polyphenols can be considered as natural antioxidants and anti-inflammatory agents, as they act not only as radical scavengers and metal chelators, but also as modulators of gene expression, intracellular neuronal signaling and metabolism, and mitochondrial function.^{115,116}

As we have seen so far, the overall results of studies exploring the effect of single nutrients or foods on PD risk are still conflicting, confirming how difficult it can be to try to identify a single protective compound among the myriad of potentially protective or harmful ones that compose a single food. Similarly, the opposite approach can also be difficult, ie, to isolate “the” active compound/compounds from a protective or hazardous food. Thus, it might be more informative to examine principle dietary patterns. From this research, it is possible to point out that countries with western dietary patterns, characterized by high consumption of animal foods, show a higher PD prevalence in comparison with countries

following a mainly plant-based diet.^{11,117} Growing evidence indicates that plant-based dietary patterns, like Mediterranean and vegetarian diets, can reduce the risk of Alzheimer's disease¹¹⁸ and PD,^{119–122} as well as plasma inflammatory biomarker concentration,^{123,124} thus potentially contributing to neuroprotection.¹²⁵

Although some parts of the puzzle of data we have reviewed thus far are in some respects lacking and largely unsatisfying, we can try to use the available information to propose a strategy of action, making the most of the complex mixture of nutrients present in plant foods.

Ensuring good nutrition

In the management of PD, a nutritional approach is warranted for many reasons. First, many studies have reported that PD patients experience a change in body weight and nutritional status. Second, nutrition seems to be directly involved in PD risk, which can manifest, after the clinical onset, as an influencing factor on the progression of neurodegeneration or as a neuroprotective effect: some foods or nutrients, mainly in diets with high intakes of animal fat and dairy products,^{83,85,95,97,98} can increase the risk, while plant-based dietary patterns showed a protective effect.^{120,122} Third, it is well established that diet modification can maximize the result of therapy with exogenous dopamine.¹²⁶

Any nutritional intervention consists of: 1) nutritional assessment (patient's nutritional history and anthropometric measures), which should be performed routinely;¹²⁷ 2) evaluation of actual individual nutritional requirements, which may change with PD progression or after surgical intervention; and 3) a sample menu, which should be correctly planned to avoid the risk of nutritional deficiencies¹²⁸ or nonacceptance caused by new dietary habits.⁵⁶ The nutritional characteristics of the main food groups are summarized in Table 1.

Ideally, the challenge of ensuring good nutrition in PD involves: proposing a dietary regimen composed of nutrient-dense food that is easy to adhere to at home through the use of commonly available food; being able to protect against nutritional deficiencies or weight modifications; and being effective in improving motor performances and possibly exerting direct or indirect neuroprotective effects. Given the limited evidence, and following the principle of precaution, the latter should include an emphasis on antioxidant phytochemical intakes (natural plant food) and the exclusion, or at least the limitation, of mercury (fish), iron, animal fat (eggs, meat, and fish), and dairy intakes. This gives rise to a diet mainly based on grains, legumes, vegetables, fruits,

Table 1 Nutritional characteristics of the main food groups

Grains: important sources of many nutrients, including fiber, several B vitamins (including B6 and folate), minerals (magnesium, zinc, and selenium), carbohydrates, and vegetable protein.
Vegetables: most vegetables are naturally low in fat and calories and are important sources of many nutrients, including fiber, folate, vitamin C, carotenoids, minerals (potassium, calcium, and iron), and phytochemicals.
Fruits: most fruits are naturally low in fat, sodium, protein, and calories, and are sources of many essential nutrients, including fiber, vitamin C, carotenoids, folate, carbohydrates, minerals (potassium), and phytochemicals.
Nuts and seeds: calorie-dense food, are important sources of omega-3 fatty acids, fiber, vegetable protein, minerals (calcium, magnesium, zinc, and selenium), vitamin E, and phytochemicals; it is important also to choose unsalted nuts and seeds to help reduce sodium intakes.
Legumes: source of carbohydrates, vegetable protein, fiber, minerals (calcium, iron, magnesium), vitamins (including B6), polyunsaturated fatty acids, and phytochemicals.
Fish and other water animals: source of protein, vitamins, minerals (iron), omega-3 fatty acids, eicosapentaenoic acid, and docosahexaenoic acid, but also saturated fats and mercury.
Dairy foods: they are the primary source of calcium in western diets, but also a source of saturated fats and animal protein, and can contain toxic compounds; only the vitamin D-fortified products are good sources of this nutrient. If consumed, it is recommended to consume them in their low-fat or fat-free forms, which provide little or no solid fat.
Meat, poultry, and eggs: source of animal protein, cholesterol, saturated fats, vitamins, and minerals (iron). A high intake of fats makes it difficult to avoid consuming more calories than are needed.

nuts, and seeds, where dairy products, eggs, fish, and every kind of meat, if present, are in limited amounts. Such a diet is called a plant-based diet: typical plant-based diets are the original Mediterranean diet and vegetarian diets.

The basic application of a balanced Mediterranean-like dietary regimen in PD patients has been already suggested. Further dietary manipulation (protein redistribution and low-protein regimens) may be considered after the introduction of levodopa therapy.¹²⁹

General recommendations

General dietary recommendations for PD patients consist of the proposal of a well-balanced plant-based diet: the menu should comply with the Dietary Reference Intakes (DRIs) for energy, macro- and micronutrients, dietary fiber, and fluids.¹³⁰ The intake of fiber, antioxidants (ie, vitamins C and E, carotenoids, other phytochemicals), and vitamin B6 in high amounts and from natural sources should always be emphasized⁶¹ as, to date, clinical trials of nutritional supplementation have provided insufficient evidence to support its routine clinical use for PD.¹²⁷ The possible beneficial effect of coffee and tea should also be taken into account in menu planning for PD patients.

Diet should satisfy energetic requirements, depending on sex, age, muscle mass, and physical activity; in PD patients energetic requirements can be increased, owing to hypertonic muscle activity and involuntary movements, even though some nonmotor symptoms can contribute to reduce effective food and energy intakes.³⁴ Although the occurrence of negative energy balance is more frequent, in some circumstances the opposite situation can occur. Periodic anthropomorphic checks, particularly in patients with advanced disease, permit the monitoring of any energy discrepancies.

Vitamin B12, calcium, vitamin D, and omega-3 fatty acids can represent critical dietary nutrients; the possibility of such deficiencies should be taken into account and prevented. Vitamin B12 (plus folate and homocysteine) and 25-OH vitamin D (25-hydroxy-vitamin D) concentrations should be checked since they are not routinely checked by primary care physicians, despite frequent deficiency in elderly people.¹²⁷

Vitamin B12

Even though research has failed to show a link between B12 status and PD,^{75,76} the role of this vitamin for CNS function has been extensively described,^{131–133} and its deficiency is common among the elderly.^{131,134} Unfortunately, ensuring B12 food sources in the diet does not guarantee the prevention of its deficiency, as malabsorption is involved in the majority of cases; many factors can compromise its intestinal absorption, from gastric conditions to the use of some common drugs.^{135,136} For this reason, it is recommended that all people over 50 years of age be supplemented. The crystalline supplement is well absorbed, unlike that which is contained in food.^{130,137} The recommended daily allowance (RDA) of vitamin B12 is 2.4 µg from multiple daily intakes.¹³⁰ The once-a-day or the once-a-week intakes require higher amounts,¹³⁸ as B12 bioavailability decreases significantly with increasing doses of single assumptions.¹³⁴ Sublingual formulation should be preferred.

Calcium

Good dietary sources have to be emphasized. Although dietary intakes below recommended levels might have negative health consequences over the long term,¹³⁹ research shows that calcium intakes are not always related to bone health in people following vegetarian diets.^{140–142} Dairy products are the primary source of calcium in western diets, but their consumption has been related to a higher PD risk.^{95,97,98} Hence, it is possible to satisfy calcium

requirements without including dairy food; some nuts and seeds (almonds, sesame), green leafy and cruciferous vegetables, not to mention dairy substitutes fortified with calcium, such as cereal and soy “milks”, represent good alternative sources.^{143,144} In the case of low calorie requirements, calcium from mineral water may provide highly absorbable calcium.¹⁴⁵ As the RDA for calcium is up to 1,200 mg,¹³⁰ some authors suggest that calcium supplementation may be useful; in most patients 500 mg per day, or in some 1,000 mg per day, is required to achieve a total intake of 1,200 mg.¹⁴⁶

Vitamin D

Apart from any possible role in PD,⁶¹ its deficiency represents a worldwide problem.¹⁴⁷ Diet can provide about 10% of the total requirement, as its natural source is endogenous synthesis and activation. Since many factors can affect the latter, the regular use of D3 or D2 supplements is recommended. The RDAs for vitamin D, which assume minimal sunlight exposure, are 600 IU (15 µg) for most adults and 800 IU (20 µg) for adults over 70 years of age.^{130,148} Some authors recently suggested that daily supplementation with 800 IU vitamin D is a practical and safe strategy which does not need prior determination of plasma levels.¹⁴⁶

Omega-3 fatty acids

Omega-3 fatty acids are provided in the form of alpha-linolenic acid (ALA) from plant sources (flaxseed, walnuts), and of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) from fish, which, however, can also contain various amounts of mercury.^{78,149} The adequate intake (AI) for ALA is 1.1 and 1.6 g/d for women and men, respectively.¹³⁰ Not only was ALA consumption found to be protective in a metaanalysis,⁹¹ it can be endogenously bioconverted to DHA and EPA in higher amounts if the intakes of total fat, saturated fat, and omega-6 fat are limited. Hence, the use of monounsaturated fats (ie, olive oil) represents a useful alternative to animal fats and to other common vegetable oils. Nevertheless, some experts suggest an AI of 250 mg/d of preformed EPA plus DHA for adults.¹⁵⁰ Although in the general population the health benefits from consuming sea- and freshwater fish are considered to outweigh the health risk associated with mercury,¹³⁷ we trust that this postulation should not be applied to PD patients, following the principle of precaution, and fish should be limited/avoided. Even if PD represents a situation where the neuroprotective role of DHA remains speculative,⁶¹ we trust that a DHA algal supplement

(200–250 mg/d) should be proposed over the consumption of ALA-rich foods. Algae supplements represent, in fact, an alternative and effective source of preformed DHA.¹⁵¹ Table 2 lists the amounts of ALA-rich foods providing about 2.5 g of ALA.¹⁵²

Levodopa-treated patients

In addition to the above general recommendations, in levodopa-treated PD patients the diet can be further implemented by limiting to the RDA the daily protein intake and, by its redistribution, concentrating protein intake in the evening meal. Preferring plant protein can also improve fiber intake; both interventions can be expected to raise levodopa bioavailability, and to improve neurological status in responder patients. Even if the literature suggests that protein manipulation should be applied to fluctuating PD patients, we trust that if the dietary intervention allows reducing total levodopa intakes, it should be applied also to nonfluctuating patients. So, responder patients are those who can reduce fluctuations and/or reduce levodopa total intakes.

Protein

Intakes should provide 0.8 g/kg,¹³⁰ which should be increased to 1 g/kg if protein is derived exclusively from plant sources.¹⁵³ In PD patients, as in the general population, average protein intake is higher than actual body requirements. An Italian study reported that PD patients had an average daily protein intake of 50% higher than the RDA (1.2 versus 0.8 g/kg).⁴⁹ Choosing plant protein supplies adequate amounts of food without the use of expensive special low-protein products.¹⁵⁴ LNAA are all indispensable amino acids, and their concentration in plant protein is lower than in animal protein. Nevertheless, plant protein can meet protein requirements when a variety of plant foods is consumed and total energy needs are met,¹⁴³ and can easily limit total protein and excessive LNAA intakes.

Total protein can be redistributed to the extent that less than 10% of the total daily protein consumption occurs

during the daytime and the rest in the evening.¹⁵⁵ PRD appears to be well tolerated by patients, and can give near-normal daytime motor function in responder subjects. Its nutritional adequacy, if total protein intake is normal, has been confirmed. Only in patients with marginally adequate diets the intakes of various nutrients, including protein, might be compromised,¹⁵⁶ as commonly happens in normal individuals when energy intakes are low.

Fiber

Natural plant foods are the sole source of fiber in the diet. In contrast with animal food, protein-rich plant food (namely legumes and nuts) also provide fiber. Fiber is important for proper bowel function, and a plant-based diet helps by reducing constipation and diverticulosis.^{157,158} As previously discussed, insoluble fiber can potentially raise levodopa bioavailability by reducing the phenomenon of constipation.³⁶ The AI range for total fiber is 21–38 g/d for adults.¹³⁰

Finally, levodopa dosing modification in relation to meals should be considered (consumption at least 30 minutes before mealtime) in order to limit the interference of postprandial gastric emptying.³⁴

Management of nonmotor complications

Nonmotor symptoms play a significant role in nutritional status and in the progression of the disease, and can heavily affect the quality of life of PD patients. Dysphagia, hyposmia, constipation, gastroparesis, gastroesophageal reflux, loss of appetite, and body weight changes are the main complications of the disease.^{127,129} Fiber-containing food provides a feeling of fullness and satiety with fewer calories, thus representing a benefit, counteracting body weight increase. On the contrary, dysphagia, loss of appetite, and body weight loss require the administration of nutrient-dense and calorie-dense food. The administration of juices in place of whole fruit and vegetables can help to fulfill the diet nutritional adequacy and provide fluids when dietary intakes are marginal. The regular consumption of nuts and seeds can provide nutrients and energy in small volumes; these foods can be mashed into creams, or ground and scattered into various dishes. Generous amounts of added oil, in the form of olive oil and small amounts of flaxseed oil, can provide concentrated energy as well as important nutrients (ie, vitamin E and omega-3 fats). If semisolid foods are required, the addition of well-cooked grains to the meal, such as millet, quinoa, and amaranth, or mashed tofu and potato, in place of specific thickening products, can increase the nutritional content of the diet without

Table 2 ALA-rich foods: amount providing about 2.5 g of ALA

Food	Amount
Flaxseed oil	1 Ts
Flaxseeds, ground	3 Ts
Walnuts	30 g (about 6 nuts)

Note: Amounts calculated using the USDA National Nutrient Database for Standard.¹⁵²

Abbreviations: ALA, alpha-linolenic acid; Ts, teaspoon (about 5 g).

significantly increasing the cost. Frequent nutrient-dense snacks, which can interfere less than a standard meal with gastric emptying and levodopa absorption, can be offered to counteract loss of appetite and gastroparesis.³⁴ Severe dysphagia may eventually require percutaneous endoscopic gastrostomy tube placement for nutritional support and more reliable PD medication dosing.

Other complications can be derived from, or can be exacerbated by, pharmacological treatment, eg, nausea, loss of appetite, and orthostatic hypotension,¹⁵⁹ the latter requiring specific nonpharmacological and pharmacological interventions if symptomatic. Moreover, levodopa therapy is responsible for hyperhomocysteinemia, independent of folate or vitamin B12 deficiency. This metabolic alteration results from methylation of levodopa and dopamine by catechol O-methyltransferase. Hyperhomocysteinemia represents a risk factor for vascular disease and, potentially, dementia and depression, and was associated with a 75% increased risk for coronary artery disease in a group of PD patients.¹⁶⁰ These findings have implications for the treatment of PD in patients at risk for vascular disease, and potentially for those at risk for dementia and depression. The reduction of levodopa total intakes, as the result of an

improvement in its bioavailability, can help to reduce these secondary effects.

Potential solutions, probable benefits

In a previous pilot study, we evaluated the short-term effectiveness of a plant-based protein-redistributed diet on levodopa-treated PD patients.¹⁶¹ The intervention diet was strictly normoproteic, and nitrogen intake came exclusively from plant sources. Patients were free to assume ad libitum amounts of plant food with the only restriction being their distribution in the daytime. The diet was supplemented with vitamin B12 and provided a redistribution of the total daily protein amount, reserving 2/3–3/4 of the total daily protein for the evening meal. After a 1-month period, the intervention group showed a significant improvement in neurological performance and stage compared with a control group of PD patients receiving their usual omnivorous protein-redistributed diet. The basic menu plan is shown in Table 3, which proposes both the omnivorous and the vegan alternatives.¹⁶¹ Choices about the composition of breakfast, lunch, and the two snacks are the same in the two patterns. At dinner, patients following the omnivorous diet could eat animal food, while in the vegan pattern the protein-rich

Table 3 Basic menu plan to limit and redistribute total protein intake: omnivorous and vegan options

Omnivorous		Vegan	
Allowed foods	Avoided foods	Proposed foods	Exchange list
Breakfast			
Tea, coffee	Milk ^a	Tea	Coffee
Bread		Bread	
Lunch			
Pasta, rice, or other cereals with vegetables and oil	Parmesan cheese	Pasta (with tomato, vegetables, olive oil, and spices)	Rice, other cereals, same amount (with vegetables, olive oil, and spices)
Bread or potatoes		Bread	Potatoes (baked, boiled), 3–4/week
Vegetables, raw or cooked (ad libitum)	Meat, ^a fish, ^a cheese, ^a eggs, ^a pulses and their products	Vegetables, raw or cooked (ad libitum)	
Fruit, raw or cooked (ad libitum)		Fruit, raw or cooked (ad libitum)	
Dinner			
Pasta, rice, or other cereals		Pasta (in vegetable soup with beans)	Rice, other cereals, same amount (in vegetable soup with beans)
Meat, ^a fish, ^a cheese, ^a eggs, ^a pulses and their products		Pulses (beans, chickpeas, lentils, peas)	Pulses soup with vegetables, whole grains, or bread
Bread or potatoes		Bread	Potatoes (baked, boiled), 3–4/week
Vegetables, raw or cooked (ad libitum)		Vegetables, raw or cooked (ad libitum)	
Fruit, raw or cooked (ad libitum)		Fruit, raw or cooked (ad libitum)	Nuts
2 snacks/day, in the morning and in the afternoon, with raw fruit (ad libitum)			
Total olive oil: 30 mL/d (2 Tbs)			
2,000 mL/d of calcium-rich mineral water			
Vitamin B12 and vitamin D supplements mandatory			
DHA algal supplement suggested			

Note: ^aFoods to consume sparingly in the perspective of a precautionary principle.

Abbreviations: DHA, docosahexaenoic acid; Tbs, tablespoons.

Table 4 1,500 kcal basic menu plan to limit and redistribute total protein intake:^a average nutritional composition for omnivorous (OMN) and vegan (VEG) options

	Omnivorous			Vegan		
	Amount (g/d)					
	Carbohydrate	Protein	Lipid	Carbohydrate	Protein	Lipid
Breakfast	18.60	4.26	3.00	18.60	4.26	3.00
Snack	21.65	0.47	0.16	21.65	0.47	0.16
Lunch	74.35	11.03	15.84	74.35	11.03	15.84
Snack	20.12	2.03	1.58	20.12	2.03	1.58
Dinner	68.52	49.17	31.32	98.76	31.59	26.39
Total	203.24	66.97	51.90	233.48	49.39	46.97
	Calories (kcal/d)					
	Carbohydrate	Protein	Lipid	Carbohydrate	Protein	Lipid
Breakfast	74.40	17.04	27.00	74.40	17.04	27.00
Snack	86.58	1.90	1.42	86.58	1.90	1.42
Lunch	297.42	44.13	142.60	297.42	44.13	142.60
Snack	80.47	8.13	14.18	80.47	8.13	14.18
Dinner	274.09	196.69	281.87	395.04	126.36	237.54
Total	812.96	267.88	467.07	933.92	197.56	422.74
Percentage of total calories	53	17	30	60	13	27
Total calories/d	1,504			1,503		
Water (mL/d)	2,752.05			2,856.0		
	Micronutrient composition (mean)/d					
Calcium (mg)	916.0			896.0		
Phosphorus (mg)	890.0			830.0		
Iron (mg)	12.2			18.0		
Sodium (mg)	530.0			112.0		
Potassium (mg)	2,212.0			3,116.0		
Fiber (g)	27.4			41.5		
Cholesterol (mg)	129.0			0.0		
Retinol Eq (µg)	721.0			1,258.0		
Vitamin C (mg)	134.0			237.0		
Vitamin B1 (mg)	0.8			0.9		
Vitamin B2 (mg)	1.4			1.1		

Note: ^aThe nutritional composition of the diet was calculated on the basis of a 1,500 kcal 1-week menu, accordingly to the Italian Food Composition Tables.¹⁶²

food was only of plant-origin. The daily nutritional composition of the two patterns, calculated on a weekly basis, is shown in Table 4.^{161,162} In PD patients not requiring protein redistribution, the same daily total foods can be consumed in other different meals.

Conclusion

Diet can contribute to the clinical status of PD patients and to the disease progression, both by altering the nutrition status and by interfering with the pharmacologic treatment. It is also probable that diet can influence the function and integrity of some neurological pathways. Energy, fluid, nutrient intake and food–drug interactions can all be causative factors, and require an optimal nutritional intervention, which should even be considered as secondary prevention. A well-balanced plant-based diet as well as (in responder levodopa-treated

patients) the limitation to RDA of total daily protein intake and its redistribution can favorably influence the disease outcomes. Since the subjective acceptability of a diet can affect long-term dietary compliance and effects, it should be highlighted that, unlike other medical conditions, responder PD patients can almost immediately experience relief from motor symptoms and side effects, which in turn make even drastic dietary changes acceptable.³⁴ No matter how drastic, however, the reported acceptability of vegetarian and vegan diets in clinical studies were found to be comparable to the other therapeutic nutritional regimens.^{163,164}

Neuroprotection represents an emerging challenge in the field of PD research, but the neuroprotective benefits we hypothesized in this paper are presently only at a speculative status, and new intervention studies are warranted to establish whether the application of a plant-based diet can

positively influence some of the different aspects modulating the development and progression of the disease. Diet can be involved in nutrition–gene interactions, ie, influencing epigenetic regulation of gene expression.⁶¹ Telomere shortening and dysfunction have been linked to age-related diseases like Parkinson's and Alzheimer's disease,¹⁶⁵ and nutrients can potentially influence telomere length. This field of research is still at a very early stage, but the results of a 5-year-follow-up small pilot study involving a group of subjects who underwent a comprehensive lifestyle intervention, including a plant-based diet, are promising. The intervention was associated with a smaller decrease in telomerase activity and a relative increase in telomere length.¹⁶⁶

Apart from any speculation, a plant-based menu seems to be a convenient way to manipulate protein intake and increase fiber intake. The reduction of dietary protein to normal requirements, the prevention of excessive LNA intake, and the redistribution of daily protein so that most protein is consumed at the evening meal, together with higher fiber intakes, can all optimize the effectiveness of levodopa treatment. Such intervention can be effective in the short-term and as well as in the long-term, allowing for the reduction of drug doses and the limitation of their iatrogenic effects (orthostatic hypotension, gastrointestinal symptoms, hyperhomocysteinemia). Improving motor performance and levodopa response can moreover delay the progression of the disease.

So, neurologists following PD patients should become experienced not only in pharmacological options, but also in the nutritional aspects of disease management. They may require the counseling of a dietitian who is expert in all implications of nutrition in PD. Patients should be periodically checked to evaluate the cost–benefit ratio of a comprehensive approach to the disease, which should no longer rely only on drugs. If strong evidence is lacking, and people need advice, the principle of precaution is always valid.

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Disclosure

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