Chapter 5
Influence of Dietary Constituents on Motor and Non-motor Symptoms in Parkinson's Disease

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, which affects about 1 % of the population over the age of 65 [1, 2] and is pathologically characterized by a progressive loss of dopaminergic cells of the nigrostriatal pathway [3, 4]. Despite considerable efforts to unravel the pathogenesis of PD, the actual trigger for the degeneration of dopaminergic and other neurotransmitter systems in PD remains unknown, which hampers the development of causative and neuroprotective treatments [5]. Numerous population-based studies have tried to identify environmental and lifestyle factors that may influence the risk for PD in order to dissect the source and potential treatments for the disease. These studies have found that smoking, coffee, and alcohol drinking lower the risk to develop PD, whereas pesticide exposure and well-water drinking are associated with a greater risk for the disease (see [6] for review). Moreover, it has been recently suggested that nicotine-containing edibles of the *Solanaceae* species, such as peppers, tomatoes, and potatoes, may reduce the risk for PD [7]. Interestingly, a potential involvement of dietary factors in the pathogenesis PD is now also supported by experimental findings from a mouse model, in which chronic, low-dose intragastric administration of the pesticide rotenone was able to reproduce the typical progression of alpha-synuclein pathology in the central nervous system seen in PD [8].

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H. Reichmann (ed.), *Neuropsychiatric Symptoms of Movement Disorders*,
Neuropsychiatric Symptoms of Neurological Disease,
DOI 10.1007/978-3-319-09537-0_5

In contrast to numerous risk studies on the impact of environmental factors on the incidence of PD, little is known about the symptomatic effects of dietary factors in patients that have already been diagnosed with the disease, which makes it hard for treating physicians to recommend specific diets to PD patients. The following chapter therefore aims to investigate scientific evidence from previous studies on the effects of dietary components on motor and non-motor symptoms of the disease. Given the multitude of food constituents that have been suggested to have beneficial effects on PD based on preclinical studies, we will concentrate on those food components, which have also been examined in clinical trials.

Antioxidants

Coenzyme Q10

One very popular dietary supplement and potent antioxidant is coenzyme Q10 (CoQ10 or ubiquinone), an electron acceptor bridging mitochondrial complexes I/II and III, which has been suggested to have potential therapeutic value in PD since mitochondrial dysfunction plays an important role in the pathogenesis of the disease [9]. After an initial 3-month open-label trial with 200 mg CoQ10 per day in ten mildly affected PD patients had found no improvement of motor symptoms [10], a parallel-group, placebo-controlled, double-blind trial in 28 PD patients suggested that daily oral administration of 360 mg CoQ10 over 4 weeks provides a mild symptomatic benefit on PD symptoms and improves color vision, but not motor function [11] (Table 5.1). We performed a multicenter, randomized, double-blind, placebo-controlled, stratified, parallel-group, single-dose trial with nanoparticular CoQ10 at a dosage of 300 mg per day, but did not find any symptomatic effects in 131 patients with midstage Parkinson's disease [12]. Nonetheless, a randomized, double-blind, calibrated futility clinical trial of CoQ10 in early untreated PD suggested that further study into disease-modifying capabilities of this component may be warranted [13]. Just recently, a placebo-controlled, double-blind clinical trial, in which 600 participants with early PD were randomly assigned to placebo, 1,200 mg/day of CoQ10 or 2,400 mg/day of CoQ10, however did not find any proof that the component would slow disease progression [14]. Based on the data presented above, there is currently no scientific evidence for an effect of CoQ10 on motor or non-motor symptoms of PD and hence no reason to recommend supplementation of CoQ10 to PD patients.

Creatine

Creatine is a naturally occurring bioenergetic compound, which is mainly taken up with meat, is essential for adenosine triphosphate (ATP) homeostasis, and has been demonstrated to have neuroprotective properties in animal models of PD [25].

Table 5.1 Randomized, double-blind, clinical trials into effects of dietary constituents on motor and non-motor symptoms of Parkinson's disease [11, 12, 14–24]

Substance	Study reference	n^a	Duration	Outcome
Antioxidants				
Coenzyme Q10	Müller et al. [11]	28	4 weeks	Mild effect on the total UPDRS and improved color vision, but no effect on motor function as measured by the UPDRS part III
	Storch et al. [12]	131	3 months	No effect on UPDRS parts II/III in midstage PD
	Parkinson Study Group [14]	600	16 months	No effect on total UPDRS in early PD
Creatine	Bender et al. [15]	60	2 years	No effect on total UPDRS, but antidepressant effect on UPDRS part I and lower requirement for dopaminergic agents
	NINDS [16, 17]	1,741	Aborted	Outcomes not reported yet, but interim analysis revealed no effect
Methylxanthines				
Caffeine	Postuma et al. [18]	61	6 weeks	Improvement on UPDRS part III and total UPDRS, but no improvement of daytime somnolence, depression, or quality of life
Natural sources of biogenic amines				
Mucuna pruriens	Katzenschlager et al. [19]	8	Single dose	Faster onset of effect on the UPDRS and longer on time without dyskinesias in comparison to conventional levodopa
Chocolate	Wolz et al. [20]	26	Single dose	No effect of dark chocolate on the UPDRS part III motor score in comparison to cocoa-free white chocolate
Polyphenols				
EGCG	Chan et al. [21]	410	12 months	Improvement on the total UPDRS compared to baseline, but no proof of neuroprotective effects
Polyunsaturated fatty acids				
Fish oil (DHA)	Da Silva et al. [22]	31	3 months	Improvement of depressive symptoms on the MADRS compared to baseline and placebo

(continued)

Table 5.1 (continued)

Substance	Study reference	n^a	Duration	Outcome
Vitamins				
Vitamin D	Suzuki et al. [23]	114	12 months	Prevention of deterioration on Hoehn and Yahr stage and UPDRS part II and improvement of subscores on PDQ-39, but no effect on motor function as measured by UPDRS part III or cognition
Vitamin E	Parkinson Study Group [24]	800	14±6 months	No delaying effect on disability requiring symptomatic treatment

EGCG (-)-epigallocatechin-3-gallate, *DHA* docosahexaenoic acid, *UPDRS* Unified Parkinson's Disease Rating Scale, *MADRS* Montgomery-Asberg Depression Rating Scale, *PDQ*-39 39-item Parkinson's disease questionnaire

[a]Number of randomized patients

After a randomized, double-blind, futility clinical trial in 200 patients with early PD had suggested that creatine should be investigated as a candidate to alter the long-term course of the disease [26], the National Institute of Neurological Disorders and Stroke (NINDS) initiated a large multicenter, double-blind, parallel-group, placebo-controlled phase III long-term study (LS-1) in patients with early, treated PD, in which 1,741 participants were randomized to treatment with either 10 g of creatine per day or matching placebo [16]. Unfortunately, the LS-1 study was stopped by the NINDS recently after an interim analysis had shown that it would be futile to continue the study since longer patient follow-up was unlikely to demonstrate a statistically significant difference between creatine and placebo [17]. Similarly, an earlier placebo-controlled and randomized pilot trial in 60 patients with early PD in Germany had demonstrated that oral creatine treatment over 2 years had no effect on overall scores of the Unified Parkinson's Disease Rating Scale (UPDRS) or dopamine transporter single-photon emission computed tomography [15]. However, this trial also revealed that creatine treatment reduced the dosages required for dopamine-replacement therapy and led to a lower UPDRS part 1 subscore, which was attributed to an antidepressant effect of this substance [15]. Although a study in major depression has indicated that creatine may lead to an augmentation of the response to antidepressant treatment with selective serotonin reuptake inhibitors [27], creatine supplementation should not be advocated as adjunctive antidepressant treatment for parkinsonian patients at the present, since corresponding studies still need to reproduce similar effects in PD patients.

Methylxanthines

Caffeine

Caffeine, a methylated xanthine that, for example, is found in coffee beans, tea leaves, and kola nuts, has been repeatedly suggested to have neuroprotective effects in PD, after numerous epidemiological studies had shown that coffee drinking is associated with a lower risk for PD [28]. Animal models of PD indicate that the advantageous effects of caffeine in PD may be mediated by antagonistic effects on the A_{2A} subtypes of adenosine receptors [29], which are predominantly expressed in the striatum [30] and co-localized with dopaminergic D2 receptors, inhibiting effects of dopaminergic transmission [31, 32].

After an open-label, 6-week dose-escalation study in 25 PD patients had found potential improvements in motor symptoms and daytime sleepiness with 400 mg caffeine per day, Postuma et al. conducted a 6-week randomized, placebo-controlled trial evaluating the effects of 100–200 mg caffeine twice daily on daytime somnolence, motor severity, and other non-motor features in 61 PD patients suffering from daytime sleepiness indicated by values of more than 10 points on the Epworth Sleepiness Scale [18]. In this study, caffeine led to a nonsignificant reduction of daytime sleepiness and did not improve sleep quality, depression, or quality of life but was associated with a significant improvement of motor function documented by a 3.2-point and 4.7-point reduction on the UPDRS part III and the total UPDRS, respectively. Moreover, anticipated side effects such as anxiety, irritability, insomnia, or worsening of action tremor were not reported more in caffeine-treated patients than in controls demonstrating good tolerability of this treatment. Although the results of this trial are in contrast to negative results of two older small-scale studies [33, 34] and still must be confirmed in separate longer-term trials, these advantageous experiences with caffeine are indeed encouraging and should prompt further research with this compound.

Natural Sources of Amino Acids and Biogenic Amines

Plants of the Mucuna *Genus*

It is already known for long that L-DOPA, the most effective antiparkinsonian agent, can also be found in several plants of the *Mucuna* genus, such as the broad bean *Vicia faba* or the velvet bean *Mucuna pruriens*, which are endemic in India and Central and South America and contain considerable amounts of natural L-DOPA [35]. After Ayurvedic medicine had already described positive effects of *Mucuna* on Kampavata [35], a disease with similarities to PD, three open-label studies involving between 18 and 60 patients reported significant improvements of PD symptoms with mean dosages of 45 g/day of *Mucuna* seed powder extract

Table 5.2 Chocolate and non-chocolate sweet consumption in patients with Parkinson's disease and household controls [44]

	PD patients	Household controls	*P* values
No. of subjects	274	234	
Sweet consumption (grams/week)			
Chocolate (mean ± SD)	100.3 ± 105.3	57.3 ± 78.1	<0.0001
Non-chocolate sweets (mean ± SD)	207.1 ± 206.9	192.5 ± 184.0	0.4542

(containing about 1,500 mg L-DOPA) [36–38]. These open-label studies were followed by a double-blind, clinical, and pharmacological study in 8 PD patients, which found a more rapid onset of action and longer *on* time with 30 g of a *M. pruriens* suspension compared to a standard dose of 200/50 mg L-DOPA/carbidopa without concomitant increase in dyskinesias [19]. Although this small pilot study suggested superior bioavailability with *M. pruriens* than with standard L-DOPA formulations and hence would have merited further investigation, its results still await confirmation by larger and longer-term studies.

Cocoa and Chocolate

Another natural source of amino acids and biogenic amines are cocoa-containing foods such as dark chocolate, which contains tyrosine, phenylalanine, tryptophan, tyramine, and β-phenylethylamine (β-PEA). Especially β-PEA may be of interest for PD, since this biogenic amine can cross the blood-brain barrier and in animal studies has shown to increase dopamine release into the synaptic cleft [39, 40]. Moreover, chocolate contains methylated xanthines, such as theobromine and caffeine, as well as flavonols, which are most likely responsible for its beneficial effects on cardiovascular disease and stroke [41–43].

Potential benefits of chocolate in PD gained our interest after we observed during ward rounds that PD patients always seemed to have chocolate at their bedside. Following this observation, we initiated a questionnaire study, in which we evaluated 498 PD patients and their partners for consumption of chocolate and non-chocolate sweets, changes in chocolate consumption during the disease course, and depressive symptoms [44]. This study revealed that consumption of chocolate was significantly higher in PD patients compared to controls, whereas consumption of non-chocolate sweets was similar in both groups (Table 5.2). Our observation prompted us to wonder whether cocoa-containing chocolate would indeed have symptomatic effects in PD. In a monocenter, investigator-blinded crossover study using cacao-free white chocolate as placebo comparator, we thus examined the effects of a single dose of 200 g dark chocolate containing 80 % of cocoa on the UPDRS motor score after 1 and 3 h in 26 subjects with moderate PD without motor fluctuations [20]. In this study, dark chocolate did not show significant improvement over white

cacao-free chocolate on motor function, which however needs to be interpreted with caution since we only used a single dose of chocolate, did not investigate the content of amino acids and biogenic amines in the administered chocolate, and did not assess potential effects on non-motor aspects of PD. At the present, we are therefore conducting another trial aiming to investigate potential effects of cocoa-containing chocolate on motor and non-motor symptoms of PD over a period of 1 week in order to account for a potential delay of uptake due to gastroparesis.

Polyphenols

Polyphenols can be found in various foods and food products, especially fruits and vegetables, coffee, green and black tea, olives, and olive oil [45]. Polyphenols have been shown to elicit anticarcinogenic, anti-inflammatory, antimutagenic, antithrombotic, and most importantly antioxidant effects [46]. Although other polyphenolic compounds, such as curcumins and baicalein, were also suggested to have neuroprotective properties in cell cultures and animal models of PD, we will concentrate on catechins in green tea, which also underwent clinical testing.

Catechins in Green Tea

Several epidemiological studies were able to demonstrate that tea drinking is associated with a lower risk to develop PD [47–50]. Green tea contains various polyphenolic compounds, among them catechins such as (-)-epicatechin, (-)-epicatechin-3-gallate, (-)-epigallocatechin and (-)-epigallocatechin-3-gallate (EGCG). EGCG is the most abundant catechin in green tea [51] and suggested to have neuroprotective properties in PD as pretreatment with both green tea extracts, and EGCG has been shown to prevent N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced dopaminergic neurodegeneration in mice [52]. Following numerous positive studies in cell cultures as well as toxic and inflammatory animal models of neurodegenerative diseases, EGCG and other catechins are now assumed to be multimodal-acting, brain-permeable, neuroprotective substances that do not only serve as antioxidants and iron chelators but also have beneficial effects on various signaling pathways, in particular the protein kinase C pathway (see [53] for review). Consequently, the Michael J. Fox Foundation decided to support a study led by Piu Chan to evaluate whether green tea polyphenols were also capable to slow disease progression in patients with early PD [21]. In this multicenter, double-blind, randomized, placebo-controlled, delayed-start study in China, 410 untreated patients with early PD were randomized to receive one of three doses of green tea polyphenols (0.4, 0.8 or 1.2 g daily) or matching placebo and evaluated with safety measures and the UPDRS over a period of 12 months. Placebo-treated patients were switched to the highest dose of green tea polyphenols after 6 months. Although the results of this study have

unfortunately not been officially published to date, the website of the Michael J. Fox foundation reports that treatment with green tea polyphenols led to a significant improvement on the total UPDRS compared to baseline after 6 months, whereas there was no difference between the early- and delayed-start group after 12 months [21]. These results would argue for an advantageous effect of green tea polyphenols on PD symptoms but also against neuroprotective properties, which would be in keeping with a previous retrospective study that did not identify disease-modifying effects of tea consumption in PD patients [54]. Since the results of the study of Chan et al. have not been published and still need to be reproduced by others, there is to date however no sufficient clinical proof to advocate green tea consumption to PD patients.

Polyunsaturated Fatty Acids

Polyunsaturated fatty acids (PUFAs) can be divided into two distinct groups according to the position of the first double bond in relation to the terminal methyl group. n-3 PUFAs and n-6 PUFAs are derived from the precursors alpha-linoleic (ALA) and linoleic acid, respectively, which both are essential to humans and cannot be synthesized de novo. One of the most important n-3 PUFAs is docosahexaenoic acid (DHA), which in the blood is mainly bound to albumin and after crossing the blood-brain barrier can be integrated into phospholipid bilayers of brain cells, where it increases membrane fluidity and contributes to optimal function of receptors and channels (see [55] for review). Although the liver has the potential to convert ALA into DHA, in vivo studies have shown that this endogenous source for the supply of DHA to the brain is rather limited compared to dietary intake of preformed DHA [56], thereby emphasizing the importance of sufficient uptake of DHA from food sources, for example, oily fish.

Various epidemiological studies have suggested that n-3 PUFAs may lower the risk for PD. In the Rotterdam Study, which investigated the interplay between the intake of unsaturated fatty acids and incident PD in a cohort of 5,289 subjects free of dementia and parkinsonism, higher PUFA intake was associated with a significantly lower risk for PD [57]. Despite not directly addressing PUFAs, another study has similarly shown that adherence to a diet with high intakes of fruit, vegetables, and fish can also significantly lower the risk to develop PD [58]. Moreover, it has been demonstrated that higher adherence to Mediterranean diet, which is known to be rich in n-3 PUFAs, is associated with reduced odds for PD, whereas lower adherence to Mediterranean diet was associated with an earlier PD age at onset [59].

Although n-3 PUFA supplementation has been shown to have symptomatic and potentially neuroprotective effects in rodent models of PD [60, 61] and to significantly reduce dyskinesias in MPTP-treated monkeys without altering the antiparkinsonian effect of levodopa [62], no clinical study has been investigating whether PUFAs would be effective to ameliorate motor symptoms of PD. Nevertheless, one clinical study has examined whether n-3 PUFA supplementation could have

advantageous effects on depression in PD. In this double-blind, placebo-controlled trial, 31 patients with PD and major depression were assigned to two groups that either received fish oil (containing n-3 fatty acids) or mineral oil capsules [22]. After 3 months of treatment, patients that had been treated with fish oil showed a significant reduction of depressive symptoms on the Montgomery-Asberg Depression Rating Scale in comparison to baseline as well as in comparison to PD patients that had been treated with mineral oil capsules. High-performance liquid chromatography analysis of fatty acid profile moreover revealed an increase of DHA in the erythrocyte membrane of patients taking fish oil, but not in patients that had been treated with mineral oil capsules. Although the results of this pilot study are encouraging, they need to be interpreted with caution since there was no difference between groups on the Beck Depression Inventory, which may be attributed to a significant placebo response on this scale. Despite effects of PUFAs on motor symptoms are unknown and the scientific rationale for supplementation of PUFAs in PD is still insufficient, we would argue that adherence to a healthy, Mediterranean-type diet may still be suggested to PD patients given the beneficial effects of this diet on cerebrovascular disease [63].

Vitamins

Vitamins C and E

One of the earliest attempts to investigate potential effects of vitamins in PD was performed by Fahn with an open-label pilot study in 15 patients suffering from early PD, who were recommended to take 3,000 mg ascorbate (vitamin C) and 3,200 IU alpha-tocopherol (vitamin E) per day [64]. The outcome of the trial was the time until patients needed symptomatic treatment with levodopa. This small study found that the combination of vitamins C and E extended the time until levodopa was needed by 2.5 years, which suggested a disease-modifying effect of both vitamins on the disease. However, the small size of the study, the lack of a control group, and its open-label design hamper the interpretation of this study. A much larger, placebo-controlled, and double-blind clinical trial was the Deprenyl and Tocopherol Antioxidative Therapy of Parkinson (DATATOP) trial, which evaluated disease-modifying capabilities of selegiline (deprenyl), a monoamine oxidase type B inhibitor, and tocopherol (vitamin E) in 800 patients with early PD [24]. In this study, treatment with 2,000 IU tocopherol per day did not lead to a delay in the need for additional symptomatic treatment. The lack of therapeutic effect of vitamin E in the DATATOP study is in agreement with epidemiological studies that did not find a significant influence of antioxidative vitamins on the incidence of PD [65, 66], whereas other studies have found that the risk for PD was reduced with higher vitamin C [67] and vitamin E intake [68–71]. Taken together, scientific evidence on the effects of vitamins C and E in PD is however not sufficient to generally recommend supplementation to patients. Given that both vitamins seem to have positive effects on

cognitive function in elderly people (see [72] for review), substitution of vitamins C and E should however be considered in those patients, in whom dietary uptake with vegetables and fruits is insufficient.

Vitamin D

Several studies have demonstrated that serum concentrations of 25-hydroxy vitamin D, the primary circulating form of vitamin D, are lower in PD patients than in age-matched healthy controls [73, 74]. Recently, a cross-sectional and longitudinal case-control study has revealed that unrecognized vitamin D deficiency is common in PD patients and that low 25-hydroxy-vitamin D3 as well as total 25-hydroxy-vitamin D levels are correlated with higher total UPDRS scores [75]. Conversely, higher plasma vitamin D levels have shown to be associated with better cognition and better mood in PD patients without dementia [76].

Surprisingly, only one intervention study with vitamin D supplementation in PD has been published until today. In this double-blind, randomized, placebo-controlled study, 114 PD patients were randomly assigned to receive vitamin D3 supplements (1,200 IU/day) or placebo for 12 months. All participants were evaluated with Hoehn and Yahr (HY) staging, UPDRS, and mini-mental state examination and asked to complete the EQ-5D and the 39-item Parkinson's disease questionnaire (PDQ-39) to assess quality of life [23]. Compared to placebo, daily supplementation with vitamin D3 for 12 months significantly prevented the deterioration of PD as measured with the HY stage, UPDRS part II (activities of daily living), and the total UPDRS and led to an improvement on some parts of the PDQ-39, whereas motor function measured by the UPDRS part III as well as cognitive function measured with the MMSE remained unchanged. Although the positive effects of vitamin D supplementation in this study may have been due to unspecific effects of vitamin D on muscle strength and balance [77] and still need to be reproduced by larger studies, it is advisable to examine the vitamin D status in PD patients and to start substitution whenever necessary, especially since PD patients have a lower bone mineral density [78] and are more prone to falls than age-matched controls [79]. Aside from motor function, future studies should also evaluate whether vitamin D supplementation is indeed accompanied by beneficial effects on cognition and mood as has been suggested by a recent study, in which higher vitamin D concentrations were associated with better verbal memory and verbal fluency and lower depression scores in non-demented PD patients [76].

Conclusion

Taken together, clinical studies on the influence of food components on motor and non-motor symptoms in PD have so far yielded largely inconclusive or negative results, which on the first look may argue against further pursuit of alimentary

approaches for symptomatic treatment of the disease. In our opinion, there is however still enough rationale for future research into this matter. At first, it needs to be acknowledged that some substances, such as caffeine and DHA, have indeed shown to have advantageous effects on motor function and non-motor symptoms of PD. Secondly, some of the negative results of previous studies must be interpreted in the light of their limited sample size and short study length, which may have prevented them from detecting potential effects on disease outcomes. Thirdly, almost all studies have concentrated on investigating single dietary components and consequently have been dependent on a single mechanism of action, e.g., antioxidative properties. In a disease with relatively slow progression and assumedly multiple underlying pathomechanisms such as PD, it may be more promising for future studies to choose a multifaceted approach and to combine multiple substances with different modes of action in order to achieve symptomatic efficacy or even disease modification. Due to their low cost, wide availability, and good tolerability, dietary components therefore remain an interesting and attractive subject for future research in PD.

Conflicts of Interest Matthias Löhle was supported by a seed grant of the Center for Regenerative Therapies Dresden (CRTD) and received honoraria for presentations from Boehringer Ingelheim, GlaxoSmithKline, MEDA Pharma, and UCB Pharma. Heinz Reichmann was acting on advisory boards and gave lectures and received research grants from Abbott, AbbVie, Bayer Health Care, Boehringer Ingelheim, Britannia, Cephalon, Desitin, GSK, Lundbeck, Medtronic, Merck Serono, Novartis, Orion, Pfizer, TEVA, UCB Pharma, and Valeant. No funding was provided for the preparation of this manuscript.

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