Parkinson's disease: the nutrition perspective

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and affects ~1% of the population over the age of 60 years in industrialised countries. The aim of this review is to examine nutrition in PD across three domains: dietary intake and the development of PD; whole body metabolism in PD; and the effects of PD symptoms and treatment on nutritional status. In most cases, PD is believed to be caused by a combination of genetic and environmental factors and whilst there has been much research in the area, evidence suggests that poor dietary intake is not a risk factor for the development of PD. The evidence around body weight changes in both the prodromal and symptomatic phases of PD is inconclusive and is confounded by many factors. Malnutrition in PD has been documented as has sarcopenia, although the prevalence of the latter remains uncertain due to a lack of consensus in the definition of sarcopenia. PD symptoms, including those which are gastrointestinal and non-gastrointestinal, are known to adversely affect nutritional status. Likewise, PD treatments can cause nausea, vomiting and constipation, all of which can adversely affect nutritional status. Given that the prevalence of PD will increase as the population ages, it is important to understand the interplay between PD, comorbidities and nutritional status. Further research may contribute to the development of interventional strategies to improve symptoms, augment care, and importantly, enhance the quality of life for patients living with this complex neurodegenerative disease.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative condition with an estimated prevalence of 1% in those over 60 years[1, 2]. First described in 1817 in 'An Essay on the Shaking Palsy', James Parkinson described both the motor and non-motor features of the condition. Parkinsonism is a symptom complex consisting of akinesia, rigidity, tremor and postural instability, the latter of which tends to emerge as the disease progresses. The onset of motor signs is often pre-dated by non-motor symptoms which encompass neuropsychiatric, sleep and autonomic dysfunction[3]. Nutrition is an often overlooked but important factor in management of the disease; dysfunction is invariably multifactorial in aetiology, different features emerge over the disease course and vary in the degree to which they impact quality of life (Figure 1).

Idiopathic PD is the commonest cause of parkinsonism and is diagnosed clinically, usually with at least two of the four clinical signs in accordance with the UK Queens Square Brain Bank criteria[4]. Imaging has a supportive role particularly where features such as early falls, lack of response to levodopa, lack of tremor, rapid progression or dysautonomia raise the possibility of an alternative diagnosis[5]. The mainstay of treatment is focussed on compensating for the primary loss of dopamine that results from presynaptic degeneration of dopaminergic cells in the substantia nigra and striatum. Dopaminergic drugs offer a gratifying response, particularly early in the disease. The heterogeneity of the disease is such that the choice of treatment regime is highly individualised.

Hoehn and Yahr described five levels of clinical disability in PD from stage 1, in which there is unilateral involvement and minimal or no functional impairment, through to stage 5, in which the individual is confined to bed/wheelchair[6]. Although these stages may not correlate with pathophysiological stages, this scale aims to have practical utility and be reproducible when scored by different clinicians. The Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), which evaluates motor signs, the impact of motor and non-motor symptoms on daily living, and motor complications, is the most widely used clinical rating scale for PD[7]. Macmahon and Thomas proposed a scale to describe the clinical course of PD from the 'diagnostic' phase; through a relatively stable 'maintenance' phase; progressing to a 'complex' phase, characterised by motor fluctuations, development of cognitive impairment and appearance of axial symptoms, including falls, freezing of gait and dysphagia; finally reaching a palliative phase[8]. It is now recognised that several symptoms, in particular rapid-eye-movement sleep behaviour disorder, constipation, anosmia and depression, known as premotor symptoms, may precede the onset of motor symptoms by many years, during what is referred to as the 'prodromal' phase[9, 10].

Pathophysiology and aetiology of PD

PD is characterised pathologically by the loss of dopaminergic neurons in the substantia nigra, thought to be due to the accumulation within neurons of aggregated forms of the protein alpha-synuclein, known as Lewy bodies. By studying post-mortem brains from individuals with and without prior symptoms of parkinsonism, Braak and colleagues described a sequential progression of neuronal damage throughout the nervous system, categorised into 6 neuropathological stages: stage 1 consisting of lesions in the dorsal motor nucleus of the glossopharyngeal and vagal nerves, which later progress to reach the brainstem, finally involving the cerebral cortex in stage 6[(11)]. Crucially, the hallmark lesions of PD were noted to develop before the clinical appearance of motor and non-motor dysfunction[(11)]. In a subsequent neuropathological study, Braak and colleagues identified Lewy bodies within the myenteric and submucosal plexuses, the collections of neurons which comprise the enteric nervous system which controls the function of the gastrointestinal tract[(12)]. This has led to the suggestion that a neurotropic pathogen, which triggers PD pathology, may enter the central nervous system via a nasal and gastric route; the so-called "dual-hit hypothesis"[(13)].

A minority of patients with PD have a Mendelian form of the disease, such that the disease is caused by inheritance of a single causative gene (e.g. SNCA, LRRK2, PARK2, and PINK1) in either an autosomal dominant or recessive pattern[(14)]. However, such cases of familial parkinsonism are rare and, in most cases, PD is believed to be caused by a combination of genetic and environmental factors. Genome wide association studies look for variability across the genome to determine whether any identified single nucleotide polymorphisms occur at a differing frequency between PD cases and controls[(15)]. Multiple loci have been potentially implicated in PD[(14)]; these low penetrance variants, which each have only a minimal impact on risk, may collectively increase an individual's risk[(15)]. Similarly, numerous observational studies have examined the impact of environmental factors on the risk of PD, including dietary factors such as alcohol consumption and caffeine intake; exposure to environmental toxins, such as pesticides; biomarkers, such as body mass index (BMI); drugs; comorbid illness; and lifestyle factors including smoking[(16)]. However, apparent associations may not reflect a causal relationship due to potential residual confounding and reverse causation. There may also be interactions between genetic and environmental risk factors such that the impact of any environmental factors is modified by the background genetic risk[(17)].

In this review we will examine nutrition in PD across three domains: dietary intake and the development of PD; whole body metabolism in PD including an overview of energy balance and musculoskeletal health; and the effects of PD symptoms and treatment on nutritional status.

Dietary intake and the development of PD

Single nutrients

Oxidative stress plays a role in the development of PD[18-20]. Antioxidant vitamins such as vitamins A, C, E and beta-carotene have established roles in reducing cell damage from free radicals, and there has been much interest in whether higher intake of these nutrients reduces PD risk. Data from the Health Professionals Follow-Up Study (HPFS) and the Nurses' Health Study (NHS) cohorts suggest lower PD risk for the highest versus the lowest quintile of dietary vitamin E[21], though at later follow-up, no association was found with vitamins C, E, or carotenoids[22]. In two Swedish cohorts, higher dietary beta-carotene intake was associated with lower PD risk, and there was also an inverse association with vitamin C and E intake but only in women[23]. Two meta-analyses suggest a neuroprotective effect of dietary vitamin E but not vitamins C and A or beta-carotene[24, 25], although these predate more recent findings from the HPFS, NHS, and the Swedish cohort studies. Elevated plasma homocysteine has been described in neurodegenerative disorders[26, 27] and evidence suggests polymorphisms in one-carbon metabolism may increase PD risk[28]. Due to the importance of B vitamins in one-carbon metabolism[26], B6, folate, and B12 have been investigated prospectively in the context of PD risk[29, 30] though the findings of these studies have been inconclusive.

The potential association between vitamin D intake and status has been explored in respect to PD risk [31, 32] and progression[33, 34] outwith of its established roles in musculoskeletal health[35]. The literature in relation to vitamin D and the risk of developing PD has been distorted by several studies[36-40], which, prior to retraction, influenced widely-cited reviews and meta-analyses[41]. A Finnish cohort study reported an inverse relationship between serum 25(OH)D and PD risk in those in the highest and lowest quartiles[31]. In contrast, a Mendelian randomization study reported a lack of support for a causal association between low 25(OH)D and risk of PD[32]. Although there is limited evidence that vitamin D is protective against the development of PD[42], low serum 25(OH)D in those with established PD may partially explain poorer musculoskeletal health[43].

Macronutrients such as dietary fat and it's individual fatty acids may influence PD risk, although there is significant heterogeneity in the literature[44-49]. Three meta-analyses, each with a different

focus, investigated the relationship between dietary fat and the risk of developing PD[50-52]. The first, by Kamel and colleagues, reported a negative association between total fat intake and PD risk[50]. While they demonstrated the same for dietary monounsaturated fat (MUFA), saturated fat (SFA), polyunsaturated fat (PUFA), α-linolenic acid and linoleic acid, associations were greatest for α-linolenic acid and weakest for SFA[50]. In contrast, Wang and colleagues found no association between total fat intake and PD risk, however, they did report an inverse relationship between PD risk and intake of total PUFA, omega-3 PUFA, omega-6 PUFA and linoleic acid[51]. The third study by Zhang and colleagues had a wider scope whereby they examined the relationship between fish and PUFA intake and PD risk in patients with mild-to-severe cognitive impairment[52]. They reported that greater PUFA intake decreased PD risk, though not through the intake of the PUFAs docosahexaenoic acid, eicosapentaenoic acid and α-linolenic acid[52]. In summary, the evidence around the intake of total fat and individual fatty acids is inconclusive and further research is needed in this area.

Food and food groups

Epidemiological evidence for the neuroprotective effects of caffeine-containing food and beverages, particularly from coffee and tea, emerged in the early 2000s[53-61]. Meta-analyses which included several of these cohorts in addition to smaller case-control studies,[62-69] have consistently found an inverse association between caffeine intake and PD risk[70-72]. Hong and colleagues also included PD cohorts and suggested that consuming caffeine may slow the rate of disease progression[72-75]. Recent case-control studies not included in these meta-analyses further support this inverse relationship between caffeine intake and PD risk[76]. The novel treatment Istradefylline, recently approved for the treatment in PD, acts at the same adenosine A_{2A} receptor as caffeine, which further supports this position[77].

Cohort studies report positive associations between dairy intake and the risk of developing PD[46, 58, 78-81]. In the HPFS and NHS cohorts, dairy intake was reported to be positively associated with PD; men consuming ≥2.9 servings/d had an 80% increased risk compared to those consuming <1 serving/d[80]. More recent data from these cohorts found total dairy intake was not significantly associated with PD, while low-fat dairy intake was[78], perhaps suggesting that the fat component of dairy foods may not increase PD risk[78]. The American Cancer Society's Cancer Prevention Study II found a positive association between dairy consumption in both sexes and PD risk; those in the top quintile had a risk ratio 1.6 greater compared to the lowest[79]. The Honolulu Heart Program which followed up men over 30 years, found those consuming the most milk (>450 ml/d) had a 2.3-fold excess of PD versus non-milk drinkers, and no association was found for calcium from dairy or non-

dairy sources[81]. In prospective cohorts in Greece and Finland, associations were also observed between milk consumption and the increased risk of PD[46, 58]. In the Finnish cohort, a positive association was reported between reduced-fat dairy products and PD risk[58]. A meta-analysis including several of these studies[46, 58, 79-81], estimated the absolute risk differences were 2-4 PD cases per 100,000 person-years for every 200 g/day increment in milk intake, and 1-3 PD cases per 100,000 person-years for every 10 g/day increment in cheese intake[82]. In turn, this was included in two umbrella reviews which considered it as Class III evidence[16] and low by AMSTAR and GRADE scores[83]. Despite the positive associations between dairy intake and PD risk, there is currently not sufficient evidence to advise against dairy consumption at a population level.

Dietary patterns

Studies which focus on single nutrients and foods risk missing the synergistic effects at whole diet level. Dietary patterns with well-established relationships to cardiovascular and metabolic health[84-86] have been investigated for their potential neuroprotective properties[58, 87-89]. While many studies used the Healthy Eating Index (HEI) and Alternate Healthy Eating Index (AHEI) to explore relationships between diet and neurological outcomes, in recent years indices based on the "Mediterranean diet" (MeDi) have generated greatest research interest[90]. Data from two US cohorts found that those in the highest AHEI and alternate Mediterranean Diet Score (aMed) quintiles were 30% and 25% respectively less likely to develop PD versus the lowest[88]; similar relationships were observed at later follow-up[91]. However, a Finnish cohort using a modified AHEI found no such relationship[58]. In a Greek population, MeDi adherence was associated with better cognitive performance and lower dementia rates[89], and subsequently it was reported that adherence was associated with fewer prodromal PD symptoms[92]. In a cohort of over 47,000 Swedish women, greater adherence to a Mediterranean diet at middle-age was associated with lower risk for PD[93]. Studies have examined a combined Mediterranean-Dietary Approaches to Stop Hypertension (DASH) Diet Intervention for Neurodegenerative Delay (MIND)[94, 95]: Agarwal and colleagues found that it appeared to reduce PD risk and slow disease progression whereas neither the Mediterranean nor DASH diets alone achieved this[95]. Moreover, in a smaller study, Metcalfe-Roach and colleagues found similar findings but in women only, while a Greek Mediterranean diet was protective in both sexes. There has been speculation that other diets such as the ketogenic, vegetarian and vegan can reduce PD risk though the evidence is limited[96]. Interest in plant-based diets and PD stems from the protective attributes of the Mediterranean or other diets rich in fruit and vegetables[97], and the apparent lower prevalence of PD outside of North America and Europe, where animal-derived foods form a smaller proportion of dietary intake.

Whole body metabolism in PD

Impaired nutritional status is a common occurrence in patients once they have established features of PD and weight loss may occur with PD progression, holding implications for treatment, quality of life and mortality. Numerous factors occur that may contribute to this process across the course of the condition, visually conceptualised in Figure 2.

Body weight

One way in which nutritional dysfunction can be observed in PD is the variation in body weight that is seen throughout the lifespan of the disease. Conflicting results have been reported in epidemiological studies likely due to the considerable heterogeneity between different populations and varying stages of the condition when studied. The investigation of weight in populations with PD poses a multitude of difficulties with confounding occurring at a population level with various levels of obesity in the country in which the study was undertaken, coupled with confounders from comorbidities such as diabetes, as well as the drug treatment regimes. Furthermore, the possible existence of specific disease phenotypes in which weight loss may feature differentially may further complicate the picture[98]. Weight loss in PD may predispose patients not only to an increased risk of malnutrition, but has been postulated to lead to the worsening of symptoms[98].

Changes in body weight may occur as a prodromal feature, before the typical symptoms of PD can be seen in an individual, however there are conflicting results. In a prospective study, Chen and colleagues demonstrated significant weight loss prior to diagnosis in over 400 patients with PD[99]. They suggested that the average weight of patients with PD was stable until shortly before diagnosis and then declined. However, in a case-control study, Ragonese and colleagues reported that no change in BMI occurred during the period preceding disease onset[100]. Both studies used different methods and assessed two geographically disparate populations some decades apart. When symptomatic individuals with PD have been studied, the literature is also inconclusive. A low BMI in symptomatic individuals with PD, relative to healthy controls, has been demonstrated in a meta-analysis of 12 studies and in over 800 patients[101]. Weight variation over the disease course is of increasing interest and is relevant clinically as the therapeutic window of the drug treatments diminishes over time and therefore dosing needs to be reviewed in light of weight changes. Yong and colleagues found progressive weight loss in PD in a 3-year longitudinal study[102], whilst a further cross-sectional study of n=125 adults with a median PD duration of 6y reported unintentional weight loss in 38% and 50%

of men and women respectively[103]. A study of a smaller cohort also suggested that BMI is low early in PD, however a retrospective chart review was used to collect height and weight data in that instance[104]. Other studies have shown no evidence of low weight or BMI in PD. Barichella and colleagues assessed BMI in n=364 Italian men and women with a mean duration of PD of 10.6y and found 65% of the cohort were overweight[105]. Similarly, when compared with controls in a cross-sectional study, overweight and obesity were more common among n=177 Mexican patients with PD[106]. Where it has been demonstrated, low BMI in PD has been shown to increase the risk of cognitive decline[107], and is a risk factor for mortality, particularly in males[108], and has also been correlated with decreased olfaction[98]. Early weight loss, occurring within the first year, has been associated with excess mortality[109].

Energy expenditure

Changes in energy expenditure have been investigated in PD. Increased energy expenditure has been demonstrated in a number of studies[110] associated in particular with rigidity and the medication "off" state which are periods of time in which symptoms significantly worsen, usually due to wearing off of dopaminergic medication[111, 112]. Further studies have shown either no evidence of increased resting energy expenditure or even a lower energy expenditure associated with the decreased level of physical activity that occurs due to disability in PD[113, 114]. Investigating this association is likely confounded by the dynamic nature of "off" and "on" medication states and the influence of varying medication states that can change throughout the course of a day.

The symptom of tremor, which predominantly occurs at rest, is a potential cause of an increase in energy expenditure. This association has seldom been investigated aside from extrapolation based on the observation of weight gain following deep brain stimulation (DBS) surgery[115]. In contrast, in studies where DBS has been carried out for the unlinked condition of essential tremor, weight gain has not been shown to be significant, disputing the link to increased energy expenditure due to excess movement from tremor[116]. Excess energy can also be spent with the excessive movement associated with dyskinesia, a fidgeting-like motion occurring due to a paradoxical surfeit of dopamine. This is common in association with levodopa therapy, with the risk worsening throughout the disease course, and is associated with decreased body weight[102]. The link of DBS with weight gain may also be a function of this negative effect of dyskinesia on weight, as one of the primary indications for undertaking DBS is to improve the nature of dyskinesia, particularly by reducing required levodopa dosing. Additionally, a central metabolic effect may be seen given the close proximity of one DBS target, the subthalamic nucleus, to the hypothalamus[117].

Energy intake

Alterations in energy intake have also been found in PD. Changes in the quality of the diet may be driven by specific cognitive changes pertaining to food selection or as part of an impulse control disorder, the latter of which may be related to dopaminergic medication[118]. Compulsive eating has been documented in PD, with one case-control study suggesting that 25% of patients with PD consumed excessive energy compared with 12% of healthy controls[119]. This can manifest as binge-eating and correlates with the presence of anxiety more strongly than medication type or dose[120]. Dietary intake in PD may be subtly affected by more than simply over-eating, with several studies suggesting a preference for sweet foods including chocolate, cakes and ice cream, even relative to household controls[121-124]. Higher carbohydrate intake, associated with lower protein, folate, magnesium and phosphorus intake has also been observed[125]. Other studies have examined the intake of food groups and low intake of fruit, vegetables and meat has been observed[121]. The dopaminergic system is highly implicated in reward and motivation, and dysfunction likely contributes to the pattern of abnormal eating seen in PD, as suggested empirically by the association of dopamine agonist therapy with overeating. It has been suggested that overeating of rewarding foods that triggers a small dopamine 'hit' may be in response to the more generalised hypodopaminergic state that defines PD[125].

Metabolic homeostasis

Evidence for dysfunction of metabolic homeostasis has been found in PD, in particular pathology affecting the hypothalamus as demonstrated in post-mortem and functional imaging studies[110]. Decreased orexin is seen in the cerebrospinal fluid of individuals with PD[126, 127], although correlation with weight has not been undertaken. Decreased ghrelin is observed in the plasma of patients with PD who experience weight loss. This suggests a degree of neurohormonal dysregulation, with an opposite relationship (an increase) usually seen with weight loss in healthy subjects[127, 128]. Decreased dynamic control of ghrelin has been demonstrated at prodromal stages, prompting the question of whether this is an early symptomatic change or causative mechanism[129]. Although conflicting results for leptin levels have been published in recent years, a recent meta-analysis suggested that this remains normal[130]. Evidence exists for a role of mitochondrial dysfunction in the aetiology of PD[131], suggesting that an intrinsic dysfunction of energy handling may exist in affected individuals, with neuronal cells particularly sensitive to abnormalities of cellular respiration.

Malnutrition, muscle, and bone

Malnutrition is common in older adults and is prevalent in PD. In a systematic review, Sheard and colleagues assessed the prevalence in over 1,100 patients with PD in 11 studies. The mean age of the PD samples ranged from 54-75y and the duration of the disease ranged from 5-13y. Irrespective of whether the patient was hospitalised, measured in a PD clinic or living in the community, the prevalence of malnutrition in PD ranged from 0-24% and the risk of malnutrition from 3-60%[132]. Other studies of either hospitalised patients[133] or those attending an outpatient clinic[134] support this finding, though different methods were used to measure malnutrition across the studies. In addition to being at increased risk of malnutrition because of the symptoms of PD, the treatment used to manage PD may also increase malnutrition risk[132].

Malnutrition is a known risk factor for sarcopenia[135-137], the age-related loss of muscle and strength [138, 139], which combined with low serum 25(OH)D in PD may negatively impact muscle strength and balance, increasing falls risk[35]. Determining the prevalence of sarcopenia in PD is complicated by a lack of consensus and a multitude of clinical definitions in widespread use. These include The European Working Group on Sarcopenia in Older Persons (EWGSOP-1, EWGSOP-2)[139, 140], Foundation of the National Institutes of Health (FNIH)[141], and International Working Group on Sarcopenia (IWGS)[142] definitions. While the European Society for Parenteral and Enteral Nutrition (ESPEN) guideline for clinical nutrition in neurology suggests that sarcopenia risk in PD is low[143] they cite only a single study that used a clinical definition of sarcopenia. This study of Italians with parkinsonian syndromes (n=364) reported a prevalence of 7% using the EWGSOP-1 definition[144]. Several more recent studies have reported higher rates. A Turkish case-control study (n=155) used EWGSOP-1 and reported a prevalence of 50% in PD and 31% in controls [145], while a Brazilian study reported a prevalence of 22% in PD using EWGSOP-2 compared to 55% with EWGSOP-1[146]. A recent Malaysian study reported a prevalence of 26% in PD using EWGSOP-2 and 4% in controls[147], greater than previous Malaysian rates based on The Asian Working Group on Sarcopenia criteria[148]. Vetrano and colleagues compared the criteria and found the prevalence of sarcopenia in PD varied between 29 and 41% in men and 18 and 33% in women, with poor agreement between EWGSOP-1, FNIH, and IGWS[149].

While in a young healthy individual, a fall from standing height would not likely result in a fracture, in PD, reduced bone mineral density (BMD)[150-152] and a higher frequency of falls increase fracture risk[43, 153-159]. Studies suggest that in PD, osteoporosis and fracture are twice as likely[150, 160, 161], and in women, PD is the strongest single contributor to fracture risk[162]. Patients with PD also appear to

have a greater prevalence of hip fracture[163-165], which is associated with increased morbidity and mortality[166, 167]. Of particular relevance to bone health, a number of case-control studies have suggested serum 25(OH)D is reduced in PD[33, 34, 43, 168-170], and those with lower 25(OH)D have a greater frequency of falls[43]. Given the vital role that nutrition plays in musculoskeletal function, further research would be valuable to specifically determine the benefit of dietary interventions on bone health and fracture risk.

The effects of PD symptoms and treatment on nutritional status

Gastrointestinal symptoms

Anosmia and dysgeusia

Anosmia is a frequently reported symptom in PD, often occurring many years before the onset of motor symptoms and affecting up to 90% of patients[171]. Ageusia is less commonly reported, however taste is heavily dependent on sense of smell and the two interlinked may affect up to 27% of patients with PD[172]. Other symptoms such as xerostomia may contribute to taste abnormalities. A decreased sense of smell and taste is known to negatively influence nutritional status[173]. On examination of the relationship between anosmia, dysgeusia and body weight, it was found that olfactory and gustatory deficits may negatively influence weight[174]. In a prospective study of patients with PD, Sharma and Turton found that 39% of patients were characterised as 'weight losers' and 60% as 'non-weight losers', with 'weight losers' more likely to be older, female and have more severe olfactory impairment[98]. Since smell is an important aspect of food appeal, it is possible that altered olfaction can negatively impact dietary intake that may be important in the pathophysiology of PD[125]. Aden and colleagues found associations between a lower intake of nutrients such as protein and olfactory function in patients newly diagnosed with PD compared to a control group[125]. Roos and colleagues suggested that hyposmia, and not hypogeusia, may contribute to weight loss in PD and hence increase the risk of malnutrition. This cross-sectional study found a significant correlation between olfactory function and BMI, but not gustatory function and BMI[175].

Dysphagia and the oral cavity

Dysphagia is common in PD, having an estimated symptomatic prevalence of 35% based on a meta-analysis of ten studies. The prevalence is further increased to 82% when considering objective measures of swallowing function[176], suggesting that asymptomatic dysphagia is widespread and occurs silently. Symptoms arise due to the disruption of swallowing at all stages of the process including the oral stage (reduced oral bolus control), pharyngeal phase (impaired coordination of

pharyngeal structures) and the oesophageal stage (impaired sphincter relaxation)[177]. Hypersalivation or conversely xerostomia that can be linked to levodopa therapy are other factors that may impair the swallowing of food[178]. Patients with PD also suffer from worse dentition than similarly aged individuals, further impairing their ability to eat, with tooth decay in turn contributed to by xerostomia[179]. Orofacial pain phenomena such as burning mouth syndrome occur at an increased prevalence in PD, causing potential distress with eating[180]. Facial and lip tremors may also occur, affecting confidence with eating[181]. Each of these factors can individually or collectively impair dietary intake and have a negative impact on nutritional status. Moreover, difficulties ingesting food may impair the intake of specific micronutrients such as vitamin D and calcium, subsequently increasing the risk of osteoporosis and fracture risk. Swallowing issues can also affect quality of life[182] which may be directly through embarrassment in social situations, or due to fear induced by choking episodes, as well as the impact that dysphagia can have on dietary intake. The presence of dysphagia is a risk factor for adverse outcomes such as pneumonia through silent aspiration, a primary cause of death associated with PD[183].

Changes to the gut microbiome

Small bowel gastrointestinal overgrowth (SIBO) has been commonly observed in PD, affecting an estimated 46% of patients and is characterised by an overgrowth of bacterial colonies beyond normally observed limits or the growth of abnormal types[184]. Diagnosis relies on the use of a hydrogen breath test to infer overgrowth, as used in studies defining prevalence in PD, although the gold standard is the physical culture of jejunal aspirate. The gut microbiome in PD is well documented to be abnormal relative to healthy controls and the overabundance of particular species are associated with risk of gastrointestinal (GI) symptoms in PD such as constipation[185]. Vitamin B12 deficiency can result from the consumption of this vitamin by anaerobic micro-organisms[186] and bacteria can disrupt bile acid which adversely affects the absorption of fat and fat-soluble vitamins[186]. Hasuike and colleagues hypothesised that bacterial overgrowth has various effects via bile acid metabolism in PD[187]. It has been suggested that serum bilirubin increases as bilirubin metabolism declines with decreases in the intestinal bacteria[187]. Simultaneously, bile acid is degraded due to increased intestinal bacteria, and lipid absorption decreases leading to low serum triglyceride levels and loss of body mass[187]. Similarly, there is decreased absorption of vitamin D aligned with a decrease in bile acid, a risk factor for osteoporosis and fractures. It is clear that consideration needs to be given to the hypothesis that some of the non-motor manifestations accompanying PD are caused by intestinal dysbiosis[187]. *Helicobacter pylori (H. pylori)* infection has been linked to PD, with higher rates of infection seen PD[188]. The benefit of eradication therapy has been addressed and is linked to improved

outcomes such as UPDRS score and "on" time[189], suggesting that untreated infection may impair levodopa absorption.

Constipation

The most commonly recognised GI symptom in PD is constipation, referring to both difficulty defecating and a decreased frequency of stool, and affects between 20-81% of patients [190]. Constipation can be seen as a prodromal symptom predating the onset of defining motor symptoms[191], and is linked to worse outcomes that include earlier onset of dementia[192]. Symptoms arise from the degeneration of brain structures involved in controlling defecatory storage and expulsion, as well as the nerves of the myenteric plexus within the bowel that control motility[193]. A similar effect on motility can also be seen in the upper GI tract, causing delayed gastric emptying[194] and both can adversely affect quality of life. Bowel motility issues also affect dopaminergic medication absorption[195], worsening motor control and cause further impact on quality of life. Constipation is a risk factor for malnutrition[196]. In a sample of community dwelling patients with PD, nutritional status was measured using two validated tools; the Subjective Global Assessment and the Patient-Generated Subjective Global Assessment (PG-SGA)[197]. Forty three percent of the cohort reported previous unintentional weight loss following diagnosis, and 15% were moderately malnourished wherein constipation was one of the symptoms reported to adversely affect dietary intake[103]. Sheard and colleagues assessed nutritional status using the PG-SGA in patients with PD awaiting DBS surgery, and of the nutrition impact symptoms listed, 58% recorded that constipation adversely affected their dietary intake over the previous two weeks[198]. In a cross-sectional study of PD in China, constipation was considered to be one of the two most important predictors of nutritional impairment[199]. Delayed gastric emptying and the resultant nausea, bloating and early satiety[194] can adversely affect appetite and in turn dietary intake, and increase the risk of malnutrition in this patient group.

The effect of non-gastrointestinal symptoms on nutritional status

Difficulty with eating

Patients with PD experience a motor disorder that affects manual dexterity and control, therefore leading to problems with the physical act of eating. Difficulty manipulating food on the plate and transporting it to the mouth accurately is seen with the risk of spillage due to tremor[200]. Increased upper limb tremor has been associated with a lower energy intake, as has the observation of fewer spoonfuls being taken during a meal by individuals with advanced stage disease[201] and represents the direct effect of the cardinal motor features of PD on the risk of malnutrition.

Cognition

In PD, cognitive impairment is a common symptom later in the disease course. Specific decline in frontal lobe function has been shown to correlate with BMI, fitting with the potential sweet food preference that can be seen in frontal executive dysfunction[202]. Cognitive impairment as it progresses becomes a risk factor for becoming dependent on others for food intake[203]. Individuals are less likely to ask for food and less likely to be able to physically prepare or access food at will due to motor disability in PD, especially in an environment that is unfamiliar such as physical care settings. Overall, the prevalence of malnutrition in care homes is high, estimated at approximately 15% worldwide[204]. This may be impacted by staffing constraints commonly encountered in such environments, and a lack of social interaction may also remove some aspects of reward associated with eating[205]. Depression is also a common occurrence in PD and may also negatively influence volition to eat with a demonstrated association of weight loss[206, 207].

The effect of treatment on nutritional status

Dopaminergic based treatments for PD primarily target motor symptoms, but are associated with recognised side-effects (Table 1). Dopaminergic medication, including levodopa, dopamine agonists and catechol-O-methyltransferase (COMT) inhibitors commonly cause nausea and vomiting which is usually transient during an initial period of acclimatisation, but may adversely affect dietary intake in the short term. Dopamine agonist medications are associated with weight gain in the long term[208, 209], potentially due to an increased incidence of compulsive eating associated with impulse control disorder. Levodopa use has conversely been associated with a decrease in body weight, although historically dopamine agonists have been used in earlier disease and may therefore simply be a function of disease staging. Weight loss is also seen with levodopa intestinal gel-infusions; however this is also a treatment reserved for late-stage disease[210]. Dyskinesia is another common phenomena related to levodopa therapy and is associated with increased weight loss[211].

Medications can also influence the handling of nutrients important for metabolism. As such, raised homocysteine levels are seen in those patients with oral levodopa dosing and decreased vitamins B12, B6 and folate levels associated with intestinal gel use[212, 213]. As described previously, DBS has been found to be consistently associated with weight gain. This may result from an improvement in dyskinesia, a primary indication for this therapy, thus reducing overall energy expenditure[214].

Nutritional status is known to affect the response to PD treatments, likely by affecting pharmacokinetic handling. Individuals with lower body weight are at an increased risk of peak-dose dyskinesia on levodopa, with a greater area under the curve exposure and longer elimination seen, necessitating consideration of weight and anticipation of ongoing nutritional care when dosing[215-217]. When normalised for body weight and adjusted for age, sex, and disease severity, levodopa has been associated with impaired nutritional status in a dose-dependent manner[218]. In addition, a cumulative dose of levodopa has been reported to be associated with micronutrient deficiency through changes in homocysteine, vitamin B6, and B12 levels[219]. Other common medications used in the treatment of PD and the effects that they may have on nutritional status are described in Table 1[220].

Conclusions and future research

We have presented an overview of nutrition in PD in this review and have covered three domains: dietary intake and the development of PD; whole body metabolism in PD, including energy balance and musculoskeletal health; and the effects of PD symptoms and treatment on nutritional status. We have highlighted areas where future work on the effect of PD on nutritional status is particularly relevant and important. Determining modifiable risk factors for PD with further research specifically on Mediterranean-style diets in particular, the MIND diet, could be vital in enhancing our knowledge of the pathophysiology of PD and therefore the development of novel treatments for the condition. Additionally, there is evidence that patients with PD are at risk of malnutrition and a better understanding of the mechanisms behind this is important in developing holistic care to optimise outcomes and quality of life.

Little is known about appetite in PD aside from limited studies that explore a tendency towards certain foods. Additionally, the burden of disability that can affect dexterity, cognitive impairment and the motor impairments that negatively impact the physical act of eating have not yet been fully determined. Tackling this need would enable techniques to be developed to assist with eating and thus improve nutritional status in this patient group. We have highlighted the studies that have sought to characterise patients' weight in the years before the onset of symptoms. Further research will allow us to understand the role of weight change in the pathophysiology of PD, addressing the question of whether weight change is integral to the underlying pathology or merely an additional early symptom. Much has been discussed about the link between PD and the gastrointestinal tract, archetyped by the Braak hypothesis[11] although currently only circumstantial evidence exists. The role played by empirically observed phenomena such as SIBO is not yet fully understood, in particular the extent to which this is important in the prodromal phase, nor is the impact of *H.Pylori* infection, where the

impact on dyskinesia is not yet clear. Adequately powered and well-designed randomised controlled trials are required to assess these links.

A better understanding of the role that nutritional factors play in aetiology will further understanding and may, in due course, contribute to developing interventional strategies to augment care and improve symptoms for patients living with this complex and multifactorial neurodegenerative disease.

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Conflict of Interest

None

Authorship

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Tables and Figures

Table 1. Common medications and their effects on nutritional status (adapted from BDA Best Practice guidance for dietitians on the nutritional management of Parkinson's, 2021[220])

Figure 1. Nutrition-related issues faced by patients with Parkinson's disease.

Figure 2. Putative representation of the dynamic and interacting factors that impact nutritional status in Parkinson's disease. GI = gastrointestinal, M & T = MacMahon and Thomas[8], H & Y = Hoehn and Yahr[6].

Table 1. Common medications and their effects on nutritional status (adapted from BDA Best Practice guidance for dietitians on the nutritional management of Parkinson's, 2021[220])

Drug	Mode of action	Side effects
Levodopa	A large neutral amino acid absorbed in the small intestine. Once absorbed, it crosses the blood-brain barrier where it is converted to dopamine, supplementing endogenous levels	Nausea, vomiting, hypotension. Associated with hyper-homocysteinaemia
Dopamine agonists	A further approach to improving dopaminergic signaling in the brain, directly activating dopamine receptors. Used less frequently due to the risk of impulse control disorder side-effects	Nausea and vomiting
MAO-B inhibitors	Used in the early stages of Parkinson's to delay the use of levodopa. Provides reduced motor fluctuations and increased 'on' time. Most commonly used as "add-on" therapy but can be effective as a primary treatment	Can cause insomnia
Anti-cholinergics	Used for the treatment of tremor or bladder symptoms. Use is limited in practice due to potential effect on cognitive function	Xerostomia, constipation and nausea
Amantadine	Antiviral agent that may increase dopamine release by blocking dopamine re-uptake and NMDA receptor antagonism	Confusion, hallucinations, insomnia, nightmares and dry mouth

MAO Monoamine oxidase Type B; NMDA N-methyl-D-aspartate