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Journal of Nutritional Health & Food Engineering

Review Article
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Nutritional supplementation, diet, and genetics and their impact on Parkinson's disease (PD), a review of studies

Abstract

A wide range of genetic and environmental factors have been implicated in the onset and progression of Parkinson's disease (PD). While studies spanning several decades have uncovered critical factors in the pathogenesis and progression of the disease, the precise etiology has remained elusive due to the complex nature of the disease. Research suggests that genetics and dietary factors are widely implicated in PD. While underlying genetic factors are critical in the onset and natural progression of the disease, nutritional status might modify the risk for developing and/or the progression of the disease. There is critical need to understand the role of nutritional factors and how they interact with genetics, in the hope of developing therapies or interventions based on nutritional supplementation. Earlier studies took a broad view of the role of diet; however, most investigators currently have striven to understand the role of specific nutrients. Nutritional status has been cited in neurodegeneration, particularly in the degeneration of dopaminergic neurons in the substantia nigra pars compacta. Manifestations of PD such as postural instability and gait disturbance are exacerbated by nutritional deficiencies. According to the findings of numerous studies, dietary antioxidants, vitamins, fats, and dietary stimulants such as caffeine clearly play a role in PD. Genetic mutations can affect the proper metabolism of vitamins, enzymes, and antioxidants, causing neuronal dysfunction which may manifest as PD. Short telomere length and other markers of oxidative stress have been implicated in PD. Glutathione deficiency, a critical marker in PD and other diseases of aging, is also linked to nutrient metabolism. These findings suggest the possibility of using nutritional supplementation to correct for altered nutrient metabolism or existing nutritional deficiencies in PD.

Keywords: parkinson's disease, nutritional supplementation, neurodegeneration, vitamins, substantia nigra

Volume 1 Issue 6 - 2014

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Received: August 25, 2014 | **Published:** December 19, 2014

Abbreviations: PD, parkinson's disease; HQL, health related quality of life; GHC, group health cooperative; UPDRS, unified parkinson's disease rating scale; VDR, vitamin d receptor; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; MPTP, 1methyl-4-phenyl-1,2,3,6 tetrahydropyridine; TL, telomere length; SOD, superoxide dismutase; ROS, reactive oxygen species; FIA, functional intracellular assay; GD, gaucher disease; NAC, n-acetylcysteine; MRS, magnetic resonance spectroscopy; LD, levodopa; CD, carbidopa; MTHFR, methylenetetrahydrofolate reductase

Background

Parkinson's disease is a chronic progressive disorder characterized by tremor, rigidity, bradykinesia, festination, dysphagia, fine motor changes, masklike faces, stooped posture, dyskinesia, among other symptoms. In most patients, the onset of the disease takes place between 50 and 65years, and has been identified as a leading cause of neurologic disorder in patients aged 60years and above. The disease occurs in males and females equally and affects people of all races.

Neurogenesis (the generation of new nerve cells) occurs shortly after birth in the olfactory bulb, prefrontal cortex, hippocampus and cerebellum. Neurogenesis ceases in these areas 0f the brain around the secondyear of life, with the sole exception the hippocampus (which facilitates the functions learning and memory). Specialized crescent shaped cells in the brain stem, known as substantia nigra (black substance), branch out from the midbrain into the left and right hemispheres of the brain. They are responsible for the release of neurotransmitters involved in balance, movement and coordination. In Parkinson's Disease, these cells are diminished significantly. When we are born, we are born with a set number of dopaminergic neurons in the substantia nigra. Like the nephrons in our kidneys, the cells of the substantia nigra cannot be regenerated. These neurons begin to die off in Parkinson's Disease. The goal of treatment in PD is to protect these neurons from dying. Parkinson's disease has a range of symptoms that impact on an individual's physical, social and mental health. This is often referred to as health related quality of life (HQL). A number of therapeutic interventions have been designed to manage symptoms of Parkinson's disease and thereby improve a patient's quality of life.[1]

Much research has been carried out to uncover the cause(s) of PD or primary Parkinsonism and other forms of the disease. However, the root cause remains inconclusive due to the complex nature of the disorder. Studies have shown that many cases of PD are sporadic,

though there have been a number of scientific findings that implicate genetic mutation as a major cause of primary PD.[2] Studies have revealed that many factors, including increased oxidative stress, varying genetic susceptibility, mitochondrial dysfunction, proteasomal dysfunction, premature apoptosis, and inflammation contribute to the pathophysiology of the disease. Environmental factors such nutritional status might modify the risk and progression of the disease.[3]

People with PD are susceptible to weight loss and malnutrition. The involuntary movements that occur in PD patients have been linked to increased energy usage. Disease symptoms and medication side-effects can also adversely affect a patient's food intake. This makes diet and nutrition a critical component of managing the condition. Understanding PD and its nutritional implications is key to the development of adequate and appropriate management strategies. This paper reviews genetics, nutritional supplementation and diet and their impact on PD.

General diet and parkinson's disease

Earlier studies that were conducted to identify the role of diet and nutrition in Parkinson's disease often took a broad view of certain nutrients, or of groups of nutrients. Relevant studies and reviews in this section have been listed below. A study was carried out by Hellenbrand et al.,[4] to establish a possible link between Diet and Parkinson's disease. The study specifically addressed the possible role regarding the intake of specific nutrients. This study compared the past dietary habits of 342 Parkinson's disease (PD) patients recruited from nine clinics in Germany with those of 342 controls recruited from the same neighborhood. The data collected was grouped using structured interviews and self-administered food-frequency questionnaires.

After adjustment for smoking, educational status, and total energy intake, patients reported a higher intake of carbohydrates compared to controls at the macronutrient level. At the nutrient level this was reflected in higher monosaccharide sugar (such as glucose and fructose) and disaccharide sugar (such as maltose, lactose and sucrose) intakes. After adjustment for energy intake, no difference was seen between patients and controls in protein and fat intake. No difference was observed between patients and controls for alpha-Tocopherol (vitamin E) intake after adjustment for energy consumption. The findings of the study suggested that if antioxidants play a protective role in this disease, then the amount provided by diet alone is not sufficient. The researchers reported that it was difficult to establish the inverse association between niacin intake and PD because there was high niacin content in coffee and alcoholic beverages, which had an inverse association in the study and further investigation was recommended to understand the association.[4]

A study was conducted by Anderson et al.,[5] to identify the role of dietary factors in PD. The study specifically looked at the role of food groups and specific foods. The purpose of the study was to investigate the link between self-reported food intake and PD in a case control study that included men and women aged between 40 and 89years.

The study identified newly diagnosed (idiopathic) PD cases from neurologist reports, outpatient databases, and computerized pharmacy databases. This was done at the Group Health Cooperative (GHC) clinics in Washington State. The GHC patient roster was used to identify control subjects who had no history of neurodegenerative disease. Structured questionnaires were used to collect dietary data from participants. The findings of the study showed that there was an increased risk of PD associated with the intake of foods rich in animal fat and foods containing vitamin D. According to the researchers the intake of foods such as fruits, vegetables, meats, bread and cereals or foods that contain vitamin A, C, E or iron was not significantly associated with PD risk. It was however noted that an increasing risk of PD was associated with the intake of vitamin A supplements.

The findings of the study were consistent with the hypothesis that there was no association between past intakes of most foods and PD risk, but confirmed an increased PD risk in association with intake of foods containing animal fat.[5] It is important to note that some of the findings of this study are considered by some experts to be inaccurate or have been challenged by subsequent research, particularly in regard to the reporting that intake of foods containing vitamin D was associated with increased PD risk. Some experts have postulated that it may have been high animal-fat foods (such as whole milk) containing high levels of vitamin D, and not the vitamin itself that was the culprit. Chen et al.,[6] prospectively investigated the association between dairy intake and the subsequent risk of developing PD among 57,689 men and 73,175 women from the Cancer Prevention Study II Nutrition Cohort from the American Cancer Society. The authors found a moderately elevated risk of PD among individuals consuming high amounts of dairy products. This risk was highest for men.

A study carried out by Powers et al.,[7] evaluated PD risks in association with dietary iron, manganese, and other nutrient intakes. The study was based on findings which show increased role of oxidative stress in the etiology of PD. This was a population-based control study conducted among newly diagnosed (n=250) and control cases (n= 388) diagnosed between 1992 and 2002 in Western Washington State. The results showed that subjects with the highest level of iron intake had an increased risk of PD compared to those with the lowest intake. Evaluation of iron and manganese intake occurring above the median showed a double risk compared to a lower intake of each nutrients. The study did not identify any strong association with fats or antioxidants. The researchers concluded that a high intake of iron, particularly when combined with manganese may be associated with increased PD risk.

A review conducted by Ames[8] suggested a role by dietary carcinogens and anticarcinogens in degenerative diseases. The review was based on earlier findings that natural mutagens and carcinogens, as well as anticarcinogens and antimutagens (free radical scavengers and antioxidants) form a bigger component of the human diet. According to the review, oxygen radicals may also act as endogenous initiators of several degenerative processes, including DNA mutation and damage, and which could be related to a wide range of conditions such as cancer, aging, and heart disease. In conclusion, the author pointed out the importance of characterizing and optimizing antioxidants in the diet for the purpose of minimizing age-related diseases and cancer.

A case-controlled study carried out by Logroscino et al.,[9] investigated the role of dietary lipids and antioxidants in Parkinson's disease. Basing their study on previous research suggesting that oxidative stress plays an important role in the pathogenesis of PD, the researchers sought to examine whether dietary intake of antioxidants or oxidative compounds had any link to PD. The researchers established a higher caloric intake in patients with PD, but this finding was similar in patients with both decreased and increased duration of their PD symptoms. Energy-adjusted intake of fat was also observed to be higher among PD patients as compared to control subjects. The intake of both proteins and carbohydrates was found

to be similar in both PD patients and controls. Fat analysis indicated that increased animal fat intake was significantly associated with PD. The researchers did not establish any association between vitamin intake and antioxidant activity. It was concluded that their finding of increased consumption of animal fat in PD patients was consistent with the previous observation that lipid peroxidation and stress are important contributing factors in the pathogenesis of PD. Vitamins from normal diet or from nutritional supplements did not show any association with antioxidant activity.

A study conducted by Rijik et al.,[10] investigated the role of dietary antioxidants in PD. The study was conducted as part of a larger community study in the Netherlands in which participants were screened for PD and asked to complete a food frequency questionnaire. The odds ratio for PD was established as follows for different antioxidant intake, adjusted for sex, age, energy intake and smoking habits: 0.5% per daily 10mg intake of vitamin E; 0.6% per intake of 1mg beta carotene; 0.9% per 100mg vit C intake; and 0.9% per 10mg intake of flavonoids. The findings suggested that a higher intake of dietary Vitamin E may offer protection against the occurrence of PD.

A review was conducted by McCarty[11] to establish if a vegan diet reduced the risk of Parkinson's disease. The review was based on the observation that a diet that is high in animal fat or cholesterol was associated with an increased risk for PD. This was contrasted with fat from plant products which did not appear to increase the risk of PD. According to the review, age-adjusted prevalence rates of PD are similar in Europe and Americas. However, among rural Chinese populations, sub-Saharan Black Africans, and Japanese groups whose diets are predominantly vegan or quasi-vegan, there appears to be lower prevalence rates of PD.

Since there is no significant difference between the prevalence of PD in white Americans and Black Americans, McCarthy hypothesized that environmental factors and not race might be responsible for the lower rates observed in Black Africans. The findings suggested that vegan diets might have a protective role with respect to the development of PD. However, the findings offered no insight on the specific components of animal fat, or protein that might mediate the increased risk of PD. The review highlighted the findings of research which shows that caloric restriction has a protective effect on the central dopaminergic neurons from neurotoxins administered to mice. This is partly achieved by induction of heat-shock proteins and it is possible that the protective mechanism in vegans follows a similar mechanism. Therefore, there is a possibility that vegan diets could benefit PD patients, by inhibiting the rate at which dopaminergic neurons are lost.[11]

Malnutrition

A study was carried out by Sheard et al.,[12] on the association between markers of disease severity and malnutrition in Parkinson's disease. The study was based on the fact that little research has been done to explore the importance of these factors in patients with malnutrition and PD. The aim of the study was to identify the determinants of nutritional status in patients with PD. The authors used the Unified Parkinson's Disease Rating Scale (UPDRS) to evaluate disease severity. The researchers recruited and administered self-report assessments to obtain information on age, PD duration, co-morbid conditions, medications, and living circumstances. The results of the study showed that 15% of the subjects were malnourished and most of these were elderly and had more severe disease. The authors found that UPDRS II, UPDRS III, and levodopa equivalent daily dose were significantly higher in the malnourished group.

Regression analysis revealed diagnosis at an older age, higher dose of Levodopa per bodyweight, greater UPDRS III score, greater depression (higher BDI, or Becks Depression Inventory) and lower anxiety (lower STAI, or Spielberger Trait Anxiety Inventory) were significant predictors of malnutrition.

The findings of the study suggested that nutrition screening should be done more often in patients with more severe disease and in PD patients with depression.

Coffee/caffeine and tea in Parkinson's disease

A study by Ross et al.,[13] investigated how coffee and caffeine intake is associated with PD risk. The study was conducted against the increased need to identify factors that either prevent or promote PD. To explore the association of dietary caffeine and coffee, the authors analyzed data from up to 30years follow up of 8,004 participants. The results collected during follow up showed a consistent decline in PD incidence with increases in amount of coffee consumed. A similar association was also observed with caffeine intake in coffee and other non-coffee sources. There was no relationship between PD incidence and other nutrients in coffee such as niacin. The study concluded that higher consumption of coffee and caffeine were associated with a reduced risk of PD.

A study conducted by Hu et al.,[14] assessed coffee and tea consumption and their association with PD risk. Many earlier prospective studies that have evaluated the association between the consumption of coffee and the risk of PD have given inconsistent results, and the authors wanted to further examine these associations. The link between coffee and or tea consumption and PD risk was evaluated in 29,335 individuals aged between 25 and 74years without a history of PD as a baseline. In a mean follow-up of 12.9years, 102 males and 98 females developed PD. The results were multivariate-adjusted and showed that the hazard ratios associated with level of daily coffee consumption (0,1-4, and $\geq$ 5 cups) were found to be 1.00, 0.55 and 0.41 in men, and 1.00, 0.50, and 0.39 in women. As for tea, the multivariate, combined findings for subjects taking $\geq$ 3 cups of tea in comparison with nondrinkers was 0.41%. The findings suggested that a lower risk of PD was associated with coffee drinking. While more tea was required for a lower PD risk.

A study conducted by Tan et al.,[15] investigated the differential effects of black versus green tea on risk of Parkinson's disease in a health study in Singapore Chinese people. The researchers utilized data from a cohort of 63,257 of Singapore Chinese men and women. Baseline data was collected through interviews utilizing structured questionnaires. The risk of PD was observed to be inversely-related to caffeine intake. Black tea, which contains up to 90mg of caffeine, demonstrated an inverse relation with PD risk but this was confounded with total caffeine intake. Green tea (typically containing no more than 70mg of caffeine) drinking had no relationship with PD. Diet was also observed not have any strong influence on the risk of PD. The researchers concluded that ingredients of black tea other than caffeine could be responsible for its inverse relation with Parkinson's disease.

Vitamin D deficiency and parkinson's disease

For decades, the medical community has understood that vitamin D promotes calcium uptake and formation of strong bones, but recent studies have demonstrated the important role of calcium in

the regulation of the immune system and in the development of the nervous system. Vitamin D is obtained from exposure to sunshine, from fortified foods such as cereals and milk, and dietary sources naturally rich in the vitamin such as fatty fish. There is growing evidence that suggests a link between low levels of serum vitamin D and Parkinson's disease. This is in addition to the finding that vitamin D is associated with many chronic degenerative diseases including diabetes, cardiovascular disease, and several autoimmune diseases.

According to recent research, vitamin D is no longer classified as a vitamin but a hormone that has both paracrine and autocrine functions that go beyond the simple regulation of calcium and maintenance of bone health. Vitamin D receptors are found in many areas of the body including muscle, spinal cord and the brain. This supports the finding that vitamin D is required in the functioning of the central nervous system and the peripheral nervous system.[16] Areas of the brain that are known to be affected by Parkinson's disease and other diseases that affect gait have been found to have vitamin D receptors and vitamin D activating hormone.

Parkinson's disease is known to affect nerve cells in many areas of the brain, mainly those that utilize dopamine to control movement. This often results in various symptoms including stiffness, slowness of gait, and tremor.[3]

A number of studies have highlighted a role for Vitamin D levels in the development and progression of Parkinson's disease. Some key findings have been listed below.

Studies on vitamin d and Parkinson's disease risk

A study was carried out by Knekt et al.,[17] to establish whether levels of serum vitamin D could be used to predict the risk of PD. This cohort study was based on a health survey conducted in Finland from 1978 to 1980, including a PD occurrence follow-up until late 2007. The study included 3,173 male and female participants. Up to 50 cases of PD occurred during the 29-year follow-up period. The levels of 25-hydroxy vitamin D were determined from frozen samples obtained and stored at baseline. An estimation of the relationship between PD incidence and the concentration of vitamin D in serum was established using the Cox model.

The findings of the study showed that individuals with higher concentration of vitamin D in their serum had a reduced risk of Parkinson disease. The relative risk identified between the highest and lowest quartiles was found to be 0.33 (95% confidence interval, 0.14-0.80) after adjusting for age, sex, marital status, education, physical activity, smoking, alcohol consumption, BMI, and month when the blood sample was drawn. The findings were consistent with the suggestion that high levels of vitamin D provide protection against PD.

A study conducted by Evatt et al.,[16] showed that there is a high prevalence of hypovitaminosis D in patients with early PD. The study was based on research findings that show patients with PD are most likely to be vitamin D deficient. However, it is not clear if having a chronic disease that results in reduced mobility can contribute to vitamin D deficiency.

The study was carried out to examine the prevalence of vitamin insufficiency in a cohort of untreated patients, suffering from early PD (diagnosed within 5years of the start of the study). The study utilized the Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism DATATOP cohort of subjects with early PD. The researchers carried out a survey study on vitamin D status in blood samples obtained from patients with Parkinson's disease and those who were enrolled in a DATATOP trial placebo group. Samples were obtained from both baseline visits and end point visits and tested for 25-hydroxyvitamin D (25[OH]D) concentration.

The findings of the study showed that the prevalence of vitamin D insufficiency (25[OH]D concentration <30.0 ng/ml) was 69.4% and 51.6% at baseline and endpoint respectively.

The researchers concluded that the prevalence of vitamin D insufficiency in patients diagnosed with early PD was equal to or higher than the prevalence reported in earlier studies. Additionally, the concentration of Vitamin D was not observed to decline with the progression of the disease. Further studies were recommended to investigate the history of vitamin D insufficiency in Parkinson's disease.

Studies on vitamin D metabolism-linked genes and association with Parkinson's disease

A study conducted by Muhlemann et al.,[18] and published in the Acta Physiologica reported that Kinase LRRK2, a gene that is mutated in Parkinson's disease, is required for vitamin D3 and phosphate metabolism. The study was conducted on the basis that mutations occurring in the Leucine Rich Repeat Kinase (LRRK2, Park8) accounts for 5% of familial and 1-2% of sporadic cases of PD. LRRK2 is expressed everywhere in the body, though high levels are found in the kidney, brain, and lungs. There is currently no clear understanding of the role of LRRK2, its regulators and targets in PD.

The objective of the study was to show that phosphate metabolism is highly disturbed in mice that lack LRRK2 or express the G2019S mutant (a common mutation seen in PD patients) and rats that are deficient in LRRK2. The findings of the study showed that levels of PTH, FGF23, and 1,25OH2-vitamin D3 were adjusted in all three animal models. Renal excretion was elevated in animals lacking LRRK2 and decreased in G2019S mutants. It was also demonstrated that expression of vitamin D receptor and the vitamin D activating and inactivating enzymes Cyp27bi and Cyp24a1 and Klotho (coligand for FGF23) were altered in many organs that expressed LRRK2. Changes in the intake of dietary phosphate in LRRk2 WT and KO mice were observed to alter phosphate and vitamin D target genes in a manner that depended on LRRK2 and the application of vitamin D3 to wild mice increased the expression of LRRK2. The in vitro inhibition of LRRK2 was observed to alter the expression of Cyp24al and NaPillb (an intestinal phosphate transporter). The findings of the investigation suggested LRRK2 played a central role in the regulation of phosphate metabolism and the various hormones involved in controlling it.[18]

Another study was conducted in Taiwan by Lin et al.,[19] to establish vitamin D receptor genetic variants and Parkinson's disease in the local population. The study was based on the findings of a recent study that showed the presence of hypovitaminosis D status and genetic variants of vitamin D receptor (VDR) in the Caucasian population. The researchers therefore sought to identify variations in a large scale Asian population.

The researchers genotyped 6 VDR genetic variants in a total of 1,492 Taiwanese subjects (700 patients with PD and 792 control subjects marched by gender or age). The findings of the study did not reveal any significant link between the studied genetic variants of

VDR and their risk of PD, and the authors concluded that the genetic variants of the VDR gene did not play a major role in the Taiwanese PD population. The findings highlighted the need for more studies on VDR and how it interacts with serum vitamin D.

A study was carried out by Torok et al.,[20] to establish the association between vitamin D receptor gene polymorphisms and PD in Hungarians. As seen in some other studies outlined in this section, the study examined the role played by the Vitamin D receptor (VDR) gene in calcium homeostasis and immunoregulation, and the link with PD and other neurological disorders. The study included 100 confirmed PD cases and 109 healthy controls sampled from the Hungarian population. The samples were genotyped for four polymorphic sites present in the VDR gene, including BsmL, Apal, Fokl and Taql. Polymerase Chain Reaction and Restriction Fragment Length Polymorphism (PCR-RFLP) was used to determine the polymorphisms.[19]

The findings of the study showed that there was an association between Fokl C allele and PD. This suggested a role played by the polymorphism in the development of Parkinson's disease in patients.[20]

Studies on the link between levels of hydroxyvitamin D and Parkinson's disease

An investigation conducted by Dean et al.,[3] established that 25-Hydroxyvitamin D depletion does not exacerbate MPTP-induced dopamine neuron damage in mice. The study was based on the new clinical findings that show a link between 250hydroxyvitamin D insufficiency (serum 25-hydroxyvitamin D [25(OH)D] levels <30ng/ml) and PD. In order to study the effects of 25(OH)D depletion on neuronal susceptibility to toxic states, the researchers induced a state of 25(OH)D deficiency in mice then treated them with dopaminergic neurotoxin 1methyl-4-phenyl-1,2,3,6 tetrahydropyridine (MPTP). No difference was found between the 25(OH)D deficient mice and control in corresponding dopamine levels or in the expression of tyrosine hydroxylase and dopamine after treatment with MPTP. In addition, the researchers did not note any difference in the expression of tyrosine hydroxylase in the substantia nigra pars compacta. The nerve cells of the pars compacta comprise a portion of the substantia nigra (Latin for "black substance") within the mid brain. Cells of the substantia nigra are blackened by the pigment neuromelanin on histologic examination. The substantia nigra is a brain structure which facilitates movement and plays an important role in reward and addiction. The degree of pigmentation increases with the subject's age. Thus the findings suggested that in this model system of Parkinsonism, the reduction of 25(OH)D levels in mice serum has no impact of the susceptibility of nigral dopaminergic neurons.

A study was conducted by Petersen et al.,[21] to investigate the role of vitamin D levels and vitamin D receptor polymorphism on Parkinson's disease in the Faroe Islands. The study sought to advance the research on the findings that both vitamin D receptor polymorphisms (VDR) and serum 25-hydroxyvitamin D levels (25(OH)D) have been associated with PD. The study sought to establish the association between 25(OH) D and 3 VDR polymorphisms and Parkinson's disease in Faroese population where prevalence has been found to be particularly high. The research employed a case-control approach in which 121 cases were investigated for 25(OH)D levels and VDR polymorphisms. This was compared to 235 controls that were randomly selected and grouped by age and gender. The results showed no significant difference in 25(OH)D levels between confirmed PD cases and the controls (P=0.49). Additionally, there were no differences observed in genotype frequencies between PD and control samples in the VDR polymorphisms investigated by researchers. It was nevertheless established that VDR Apal/AC genotype was highly associated with 25(OH)D levels (P=0.01). In conclusion, the researchers did not rule out a weak association between PD and vitamin DS polymorphisms ad 25(OH)D levels. However, the findings were not sufficient to explain the doubling of PD prevalence in Faroe Islands using polymorphisms investigated in the VDR gene or levels of 25(OH)D. Further research was therefore recommended.

A study was carried out in Iran by Moghaddasi et al.[22] to identify the concentration of serum 25-hydroxyvitamin D3 concentration in Iranian patients diagnosed with PD. The study sought to establish the level of vitamin D in patients with PD and further identify how it relates with severity of the symptoms observed. The researchers recruited 83 patients with PD and used electrochemiluminescence immunoassay (ECLIA) to measure the level of 25-hydrovitamin D [25(OH)D3]. Findings of the study showed that the concentration of 25(OH)D3 was lower in PD cases compared to the normal group. The study also associated lower levels of 25(OH)D3 with abnormal posture and postural instability.

Studies on the link between neuronal function, vitamin D and Parkinson's disease

A pilot study was conducted by Peterson et al.,[23] to establish the relationship between balance control and vitamin D in Parkinson's disease. The study was based on the background that balance problems are a major cause of morbidity and mortality in patients suffering from Parkinson's disease. Balance function and vitamin D concentration were quantified in a series of patients with PD in an observational, cross sectional study. This was necessary for the establishment of relationships and selection of outcomes measures for vitamin D intervention study. The study established an inverse correlation between vitamin D concentration and PD severity as measured by the motor Unified PD rating scale. The findings of the study were consistent with the hypothesis that vitamin D is essential for balancing in PD patients.

A study was conducted by Peterson et al.,[23] to establish the association between Memory, mood, and vitamin D in persons suffering from Parkinson's disease. The study was based on the findings of recent studies which show that vitamin D plays a significant role in the functioning of the central nervous system. As shown in animal studies, vitamin D is crucial in the development of neurons, stabilizing of the functions of mitochondrial functions, antioxidation, and the up regulation of neurotrophic factors. The objective of the study was to establish the relationship between serum vitamin D and neuropsychiatric function in individuals with PD. The study was conducted as an add-on to a longitudinal survey researching on the neuropsychiatric performance and serum 25-hydroxyvitamin D in PD patients. The baseline neuropsychiatric performance and serum 25-hydroxyvitamin D were examined for up to 286 confirmed PD cases.

Several measures were administered, including global cognitive function (MMSE, MOCA, Mattis Dementia Scale), Verbal Memory (Hopkins Verbal Learning Test), Fluency (Animals, Vegetables, and FAS words), visuospatial function (Benton Line Orientation) Executive function (Trails Making Test and Digit-Symbol Substitution), Depression (Geriatric Depression Scale [GDS]) and PD severity

(Hoehn & Yahr and Unified PD Rating Scale). The researchers used a multivariate linear regression to assess how vitamin D concentration related to neuropsychiatric function. This was done in both demented subjects and non-demented subjects.

Numerous neuropsychiatric tests showed better performance with higher vitamin D concentrations in the non-demented subset of the cohort. In particular, there was a significance association between vitamin D concentration with verbal memory and fluency. A correlation was also established between depression scores and the non demented subset. The researchers concluded that higher levels of vitamin D is essential for better cognition and better mood in PD patients without dementia.[24]

Vitamin D supplementation and Parkinson's disease

A randomized, double-blind, placebo-controlled trial of vitamin D supplementation in PD was carried out by Suzuki et al.[25] The study was based on the findings of a previous study conducted by the same researchers and which showed that a higher serum 25-hydroxyvitamin D [25()H)D] concentrations and the vitamin D receptor (VDR) FokI CC genotype were linked with milder cases of PD. The objective of the study was to evaluate whether vitamin D3 supplementation inhibited the progression of PD on the basis of patient VDR groups. During the study, patients diagnosed with PD were randomly selected to receive vitamin D3 supplement or a placebo for a period of 12months in a double blind setting.

The outcomes were measured as clinical changes from baseline and the percentage of patients indicated with a worsening modified Hoehn and Yahr (HY) stage and the Unified PD Rating Scale (UPDRS). The findings of the study showed that vitamin D3 had a significant effect in the prevention of the deterioration of the HY stage in patients as compared with placebo. VDR FokI genotypes were seen to modify the effect of vitamin D3 on the changes that take place in the HY stage. The findings led to the conclusion that vitamin D3 supplementation, may stabilize PD for a short time in cases where patients have FokI TT or CT genotypes without resulting in hypercalcemia.

Telomere length in Pd

A study conducted Watfa et al. investigated telomere length and different markers of oxidative stress in patients suffering from PD. The study was based on the findings of several studies that show an association between short telomere length (TL) with high oxidative stress in several age-linked diseases. PD is an age-related disease and even though the pathogenic mechanism is not well understood, oxidative stress is thought to play a role. The study assessed TL and other biomarkers of oxidative stress in patients suffering from PD in comparison to age-matched control subjects. 20 PD subjects and 15 >65years of age controls were investigated. Southern blotting was used to measure TL in samples from white blood cells. Superoxide dismutase (SOD) activity and plasma levels of the level of protein carbonyls and glutathione were measured. The results showed a trend for lower TL in PD subjects. There was however no significant difference established between the groups in relation to oxidative stress markers. Age was a key determinant in telomere shortening in the controls. In PD, the concentration of carbonyl proteins was a key factor in telomere shortening, and a negative association was established between plasma carbonyl protein levels and SOD activity. The researchers concluded that the absence of age-related telomere attrition in PD patients could be due to telomere regulation by other mechanisms.[26]

CoQ-10 deficiency and Pd

A study was conducted by Mischley et al.,[27] to investigate Coenzyme Q10 deficiency in patients with PD. The study was based on the background that several studies have shown that reactive oxygen species (ROS) play a role in the pathophysiology of PD, and that many clinical antioxidant trials are underway in PD patients but facing challenges from the lack of peripheral markers for antioxidant research.[27] In the study, 22 patients diagnosed with PD were selected to undergo Functional Intracellular Assay (FIA) between 2004 and 2008. Each finding was compared to four controls matched by gender and age (8=88) in four random and separate iterations utilizing lab data collected around the same period of time. The functional deficiency in the antioxidant nutrients (coenzyme Q10, glutathione, vitamin E, selenium and alpha-lipoic acid) was determined using logistic regression. Chi (2) test was also used in the comparison of the cases with functional deficiency and that of the controls.

The findings of the study showed that compared to cases, PD patients showed higher odds of Q10 deficiency. This was not however the case for selenium, Lipoic acid, Vitamin E or glutathione (P>0.05). Coenzyme q10 deficiency was also found to be significantly higher in cases compared to controls. The researchers conclude that deficiency of Coenzyme Q10 as established via FIA should be investigated as a candidate biomarker for antioxidant status in PD.[27]

A study conducted by Yang et al.,[28] investigated whether a combination therapy with coenzyme Q10 and creatine produces additive neuroprotective effects in models of Parkinson's and Huntington's diseases (HD). Creatine and Coenzyme Q10 are known to improve mitochondrial function and cellular bioenergetics, this together with their properties as antioxidants, makes them suitable agents for neuroprotection in neurodegenerative diseases. The researchers examined whether an additive neuroprotective effect in MPTP mouse model of PD, 3-NP rat model of HD, and the R6/2 transgenic mouse model of HD could be achieved by combining CoQ10 and creatine. The study showed that the combination of the two agents produced additive neuroprotective effect against dopamine depletion in the striatum and loss of tyrosine hydroxlase neurons in the substantia nigra pars compacta (SNpc) following a chronic subcutaneous administration of MPTP. A significant reduction in lipid peroxidation and pathologic alpha-synuclein accumulation in the substantia nigra pars compacta of the mice that were treated with MPTP was achieved following the combination treatment. The researchers also noted additive neuroprotective effect in the reduction of the volume of striatal lesion produced by subcutaneous 3-NP administration. A significant effect in blocking 3-NP mediated harm to glutathione homeostasis was also achieved through the combination treatment, and thereby reducing lipid peroxidation and DNA oxidative damage in the striatum. The combination treatment also showed an improvement in the motor performance and prolonging survival in the transgenic R6/2 HD mice.

The findings of the study suggest that by using a combined treatment of CoQ-10 and creatine, better treatment of neurodegenerative diseases such as HD and PD can be achieved.[28]

Glutathione and Parkinson's disease

Glutathione implication for health

A review was carried out by Wu et al.,[29] to establish the implications of glutathione (GSH) metabolism for health. The review

was based on findings that show adequate protein availability is crucial for the maintenance of GSH homeostasis in both humans and animals. This is particularly true in the synthesis of GSH from Glutamate, cysteine, and glycine through the activity of gamma-glutamycysteine synthetase, cytosolic enzymes and GSH synthetase. Additionally, cystine (both enteral and parenteral), N-acetyl-cysteine, methionine, and L-2-oxothiazolidine-4-cardoxylate have been found to be effective precursors of cysteine for use in tissue GSH synthesis.

The review also identified the critical role played by glutathione in nutrient metabolism, regulation of cellular events and, most importantly, in the antioxidant defense. Glutathione deficiency contributes to oxidative stress, which plays a significant role in the aging and pathogenesis several diseases, including Parkinson's Disease, cystic fibrosis, sickle cell anemia, HIV/AIDS, cancer, heart attack, diabetes, stroke, seizure, Alzheimer's disease, and Kwashiokor.[29]

New knowledge has since been developed to show a deeper understanding of the regulation on glutathione metabolism and PD.

Glutathione deficit and Parkinson's disease

Ballatori et al.,[30] conducted a review on glutathione dysregulation and the etiology and progression of human diseases. The review was based on the finding that GSH plays an important role in a multitude of cellular processes, including differentiation, proliferation, and apoptosis, and therefore, homeostatic disturbances in GSH are implicated in the etiology and/or progression of a number of diseases, such as cancer, aging diseases, cystic fibrosis, inflammatory, cardiovascular, immune, metabolic, and neurodegenerative diseases. However, the pleiotropic effects of GSH on cellular functions have made it difficult to clearly pinpoint the role of GSH in the onset and/or expression of human diseases, though there is much progress in that direction. Studies have shown that the level of GSH, turnover rates, and oxidation state can be altered by acquired or inherited defects in enzymes, transporters, signaling molecules, or transcription factors that play a role in its homeostasis, or following exposure to metabolic intermediates or reactive chemicals. Deficiency in GSH or a decreased GSH/glutathione disulfide ratio is largely manifested through increased susceptibility to oxidative stress, and the damage that occurs is thought to play a role in diseases such as cancer, Alzheimer's disease, and PD. The immune system is also affected by GSH imbalances and this plays in the aging process.[30]

A study was carried out by Kaur et al.,[31] to investigate how the increased labile iron pool due to glutathione depletion in immortalized midbrain-deprived dopaminergic neurons means for PD. The study was based on the finding that GSH depletion is one of the events detected early in the substantia nigra of PD patients. However, it remains unknown if it is a causative agent in the ensuing molecular events associated with the disease. According to the researchers, the increase in the cellular labile iron pool (LIP) is independent of neither iron regulatory element/iron regulatory protein (IRP/IRE) nor hypoxia inducible factor (HIF) induction but is dependent on both H(2)O(2) and protein synthesis (Kaur, Lee, Ragapolan, & Andersen, 2009). The findings of the study suggested that a novel mechanistic link between dopaminergic glutathione depletion and increased iron levels based on translational activation of TFR1.[31] This could have a role in the neurodegeneration seen in PD in which reduction in GSH and elevations in iron are evident.

A review was conducted by Johnson et al.,[32] on the dysregulation of glutathione homeostasis in neurodegenerative diseases. The review was conducted against a background of increasing implication of glutathione-dependent enzyme activities in the induction and progression of neurodegenerative diseases such as Alzheimer's PD, HD, Friedreich's ataxia, and amyotrophic lateral sclerosis. The review focused on the provision of background on the synthesis, transport, and regulation of GSH, particularly in the brain. The review also included a brief description of the role of glutathione in cellular maintenance and survival, and the functions of different GSH enzymes. The review established that the major contributors to initiation and progression of neurodegenerative disease to be oxidative stress, protein misfolding, and protein aggregation.[32] The mechanisms of glutathione and/glutathione-dependent-dependent enzyme regulation that play a role in the pathogenesis of neurodegenerative diseases were discussed.

A study was carried out by Sian et al.,[33] to examine the alterations in glutathione levels in Parkinson's disease and other neurodegenerative disorders affecting basal ganglia. During the study, researchers measured reduced GSH and oxidized GSH (GSSG) levels in various brain areas, including substantia nigra, putamen, caudate nucleus, cerebral cortex, and globus pallidus in patients dying with PD, multiple system atrophy, progressive spranuclear palsy, and HD against controls with no neuropathological changes in the substantia nigra. The findings showed that the levels of GSH were reduced in the substantia nigra of PD patients (40% compared to controls) and GSSG levels marginally elevated. No changes were observed in other brain areas. The only significant change observed in multiple-system atrophy was elevation in glutathione (196%) together with a reduction in GSSG (60%) in the globus pallidus. The only change seen in progressive supranuclear palsy was a reduction in the level of GSH in the caudate nucleus (51%). In spite of the fact that the substantia nigra had more profound cell loss in PD, progressive supranuclear palsy, and multiple-system atrophy, the level of glutathione in the substantia nigra was reduced significantly in PD. The findings showed that the GSH changes observed in PD are not solely due the death of nigra cells or explained by drug therapy. The modified GSH/GSSG ratio in the substantia nigra observed in PD is consistent with findings that have shown oxidative stress being a major component in the pathogenesis of nigral cell death in PD.[33]

A study conducted by Groger et al.,[34] investigated dopamine reduction in the substantia nigra of PD patients using in vivo magnetic resonance spectroscopic imaging. The study sought to confirm metabolic changes in the substantia nigra of PD patients which had traditionally been investigated using different molecular-pathological examinations. The researchers aimed at measuring the in vivo alterations using a three-dimensional magnetic resonance spectroscopic imaging. During the study, 21 PD patients and 24 controls were examined using the magnetic resonance spectroscopic imaging at 3 Tesla. The LC model was used to analyze the spectra of rostral and caudal regions of the substantia nigra. The in vivo spectra were produced by an adjusted data set with macromolecules and metabolites. The researchers established a significantly decreased N-acetylaspartate, creatine, choline, glutathione, myo-inositol, and dopamine concentrations in PD patients as compared to the controls. However, the level of glutamine +glutamate, Y-aminobutyric acid, and homovanillic acid were slight enhanced. The results showed clear biochemical profiles between caudal and rostral substantia nigra in the two groups. The researchers concluded that reduced levels of dopamine and N-acetylaspartate concentrations resulted from the progressive degeneration of dopamine-producing neurons in the substantia nigra. The decrease in the level of creatine was interpreted as an impairment in energy metabolism due to a dysfunction in the mitochondria. The lower levels of glutathione were interpreted as a result of oxidative stress.[34]

A study was conducted by Elokda et al.,[35] to establish the effects of exercise induced oxidative stress on glutathione levels in Parkinson's disease during off and on medication. The study was conducted on the findings that show resting plasma GSH levels to be lower in people suffering from PD in comparison to other neurological conditions. Furthermore, medications used in the treatment of PD have been shown to cause a further depletion in resting plasma GSH. Acute exercise is known to produce oxidative stress which is detected by lower levels of GSH. The study aimed at establishing how PD responds to acute exercise stress and how medication affected such responses. The researchers subjected 14 men with PD and 14 men without PD to an exercise stress test. The subjects with PD did the test while off PD medication for 12 hours and repeated it one week later while on PD medication. GSG and GSSG samples were collected via blood at rest following peak exercise together with peak VO (2). The results showed that the levels of GSH and the GSH:GSSG ratio were found to be significantly lower in the PD- on medication and PD-off medication compared to the controls. The level of GSSG was found to be significantly higher in both medications at rest and peak exercise as compared to controls. Comparison between PD on medication vs. PD off medication and peak exercise, the PD on medication was found to have lower levels of GSH, and a lower GSH: GSSG ratio but a higher level of GSSG. VO (2) was found to correlate positively with the levels of GSH. Thus the findings showed that PD patients had lower levels of plasma GSH compared to healthy people at rest and peak exercise.[35]

A study was conducted by Chen et al.,[36] to establish whether increased oxidative damage in peripheral blood correlates with severity of PD. Basing their research on the findings that show neuronal dysfunction due to increased oxidative stress in PD patents, the researchers sought to investigate whether the pathological changes that occur in the brain of PD patients are also present in peripheral tissues. Measures of leukocyte 8-hydroxydeoxyguanosine (8-OHdG), erythrocyte glutathione peroxidase (GPx), plasma malondialdehyde (MDA) and plasma vitamin E (vit E) were done in 211 PD subjects and 135 healthy controls. The results showed an elevation in the level of Leukocyte 8-OHdG and plasma MDA, whereas the level of plasma vitamin E and erythrocyte GPX were reduced in PD patients in comparison to the healthy controls. After adjusting for environmental factors, logistic regression showed that PD severity had an independent correlation with 8-OHdG and MDA level, and inversely correlated to GPx activity and vitamin E level. The results suggested an increase in oxidative damage and decreased antioxidant capacity in the peripheral blood, and a significant correlation between leucocyte 8-OHdG levels and the severity of the PD disease.[36]

Glutathione genes and Parkinson's disease

A study was conducted by Wang T et al.,[37] to establish the association between Glutathione S-transferase M1/Glutathione S-transferase T1 polymorhisms and Parkinson's disease. The study was based on the extensive but inconclusive findings that show Glutathione S-transferase M1 (GSTM1) and Glutathione S-transferase T1 (GSTT1) as potential candidate genes for the risk of PD. The researchers used an updated meta-analysis to determine the effect of GSTM1 and GSTT1 polymorphisms on PD. The researchers used a fixed-effect model to calculate the combined odds ratio of different ethnicities, at 95 confidence intervals. The researchers evaluated the homogeneity of the studies included in the evaluation. There was no association established in the analysis of different races, except for a weak association that was established in the GSTM1 variant in Caucasians.[37]

Treatment of PD with glutathione

A randomized, double-blind pilot evaluation of intravenous glutathione treatment in PD was conducted by Hauser et al.[38] The objective of the study was to investigate the safety, tolerance, and preliminary efficacy of intravenous glutathione in PD patients. The study was carried out as a randomized, double-blind, placebo-controlled trial in subjects with PD whose motor symptoms were not adequately controlled with their currently used medication regimen. A random assignment of three times a week intravenous administration of glutathione 1,400 mg or placebo for four weeks was conducted on the subjects. A total of 21 subjects were included, 11 to glutathione administration and 10 to placebo. One participant in the glutathione group withdrew due to personal reasons prior to the start of the assessment. Glutathione was well tolerated as no adverse effects were reported in the group. No significant differences were established in the Parkinson's disease Rating Scale (UPDRS) scores. During the four weeks of administration, UPDRS ADL + motor scores showed improvement by a mean of 2.8 units more in the glutathione-administered group (P=0.32). This however worsened by a mean of 3.5 more in the glutathione group in the subsequent 8 weeks (P=0.54). Therefore, preliminary data of intravenous treatment of PD with glutathione indicate a possibility of mild symptomatic effect, though this remains to be studied in a larger group.[38]

A review was conducted by Jin et al.,[39] on mitochondria-targeted antioxidants for treatment of PD both in clinical and clinical phases. The review was based on the findings that show that mitochondrial dysfunction and oxidative stress play a central role in the dopaminergic neurodegeneration in PD. Therefore, therapies that are targeted at the mitochondria to improve mitochondrial function might be useful in the treatment and prevention of PD. The review elaborated on the recent developments relating to the antioxidants that are targeted to the mitochondria and the potential application in correcting mitochondrial dysfunction in PD.[39]

Effect of N-Acetylcysteine on glutathione levels in PD

A study conducted by Holmay et al.,[40] established that N-Acetyl cysteine boosts the brain and blood levels of glutathione in Gaucher disease (GD) and PD. The study utilized adult subjects, 3 with PD, 3 with GD, and 3 healthy controls. 7-T magnetic resonance spectroscopy (MRS) was used to measure baseline brain GSH concentrations. The baseline ratios of reduced to oxidized GSH were established for every subject. The findings of the study showed that N-acetylcysteine (NAC) increased the redox ratios of PD in the blood with those diagnosed with GD, PD and the healthy controls and this was followed by an increase in the levels of brain GSH in all subjects. The study indicated that with the use of MRS, it was possible to measure and monitor the increase in levels of GSH in the brain following intravenous administration of a single dose of NAC. Thus MRS can be used in the establishment of dose regimens for clinical trials of the antioxidant therapy in GD and PD, in addition to other neurodegenerative diseases.[40]

Cysteine as a precursor of glutathione through levodopa action

A study was conducted by Muller and Muhlack[41] to investigate the effect of Levodopa intake in patients suffering from PD. The study was carried out on the background the redox milieu is established by thiol homeostasis and therefore scavenging for free radicals like GSH. The process of forming GSH occurs following a combination between I-glycine and glutamine acid. Additionally, an up-regulation of free radicals is identified as a major feature in neurodegeneration.

Levodopa (LD) is thought to support the synthesis of free radicals through the degradation of the dopamine derivative in mitochondria. The researchers therefore purposed to investigate the impact of LD on the turnover of free cysteine in plasma. 200mg LD/50mg carbidopa (CD) was administered to 13 PD subjects. The levels of LD and free cysteine in plasma were measured before and after the LD/CD application. As expected, the level of LD increased with the decay of cysteine. The researchers concluded that the decrease in cysteine may be due to an up regulation of GSH synthesis in response to the enhanced presence of free radicals associated with the turnover of LD in mitochondrial monoaminooxidase.[41]

MTHFR polymorphism, homocysteine levels and Parkinson's disease

A review was done by Garilli[42] on MTHFR Mutation: A missing piece in the chronic disease puzzle. Methylenetetrahydrofolate reductase (MTHFR) is very important enzyme that plays a critical role in numerous biochemical processes. Non optimal production and utilization of MTHFR has been linked to an increased risk of several chronic diseases including stroke, myocradial infarction, cancer, many neuropsychiatric diseases, inflammatory bowel disease, and a number of congenital defects. Mutations in MTHFR have been associated with neuropsychiatric conditions because of the indirect involvement of MTHFR in production of dopamine, norepinephrine, and serotonin, in addition to adverse effects of hyperhomocysteinemia. According to the review, mutations of the MTHFR gene has been linked to PD, Alzheimer's disease, bipolar disorder, Schizophrenia, and vascular dementia.[42]

A study conducted by Yasui et al.,[43] measured the level of cysteine and homocysteine in 90 patients with PD and with the MTHFR c677T (T/T) genotype. The results showed that the levels of homocysteine were enhanced by 60% in patients who were treated with Levodopa. The highest elevation occurred in T/T genotype patients. The researchers concluded that MTHFR genotype, Levodopa and folate might be associated with increased homocysteine.[43]

A study conducted by Nakaso et al.,[44] reported that hypertrophy of IMC of carotid artery in Parkinson's disease is associated with L-DOPA. Homocysteine (Hcy), and MTHFR genotype. The study was prompted by the increased interest in understanding the association between hyperhomocysteinemia and PD. According to the study, a mild hypertrophy of the carotid artery intima –media complex (IMC), a systemic atherosclerosis marker, is seen in patients with PD in comparison to normal subjects. Hypertrophic IMC was observed in patients following a lengthy treatment with L-DOPA. In cases that had a hypertrophic IMC of the carotid artery, an elevation in the plasma levels of Hcy associated with C677T genotype of 5,10-methylenetetrahydrofolate reductase (MTHFR) was witnessed.[44] The findings of this study suggest that atherosclerosis can be enhanced in PD patients by hyperhomocysteinemia via the C677T MTHFR genotype and a prolonged L-DOPA treatment.

A review was carried out by Mattson and Shea[45] on folate and homocysteine metabolism in neural plasticity and neurodegenerative disorders. This was based on the finding that, among other functions, folate plays a role in remethylation of homocysteine, which can in turn induce breakage of DNA, oxidative stress, and apoptosis (programmed cell death). Dietary folate regulates programmed cell death and neurogenesis. The authors evaluated studies that link folate deficiency, increased homocysteine and its association with neurodegenerative diseases such as PD, Stroke and Alzheimer's disease. Genetic and clinical data were cited as critical pointers to the role of homocysteine and folate in pathogenesis of psychiatric disorders.[45]

A study conducted by Religa et al.,[46] sought to establish the effect of duration of PD on hyperhomocysteinemia. The study focused on the influence of different factors such as levodopa dose, duration of therapy and disease, in addition to MTHFR polymorphism and other environmental factors. Among other findings, the researchers established that PD patients subjected to levodopa treatment showed elevated levels of homocysteine in plasma when compared to the control subjects, the levels did not however depend on the doses of levodopa.[46] The researchers concluded that hyperhomocysteinemia was linked with levodopa treatment, duration of PD and probably with the PD itself.

A study conducted by Todorovic et al.,[47] sought to clarify whether Levodopa treatment was necessary for homocysteine serum levels in PD patients with MTHFR C677T genotype. The total level of homocysteine (tHcy) and MTHFR C677T in serum were investigated in both PD patients who were treated and those not treated with levodopa, as well as healthy controls matched by gender and age. The results of the study showed that tHcy was elevated in both levodopa-treated and untreated PD compared to the controls.[47] The findings indicated that MTHFR C677T was a key factor in the occurrence of hyperhomocysteinemia in patients with Parkinson's disease, regardless of levodopa treatment status.

Park 7/ Dj -1 gene and Parkinson's disease

PARK7/DJ-1 is a gene that codes a protein belonging to peptidase C56 proteins family. PARK7 is part of four chromosomal loci (PARK2, PARK6, PARK7, and PARK9) which are linked to autosomal recessive, early onset of PD.[48] The protein functions as positive regulator of androgen transcription. It also acts as redox-sensitive chaperone, mitochondrial regulator, and oxidative stress sensor, protecting neurons from cell death and oxidative stress.[48] Defects in this gene are thought to result into autosomal recessive early onset of PD7.

A review conducted by Bonifati et al.,[49] sought to understand the pathogenesis of PD by linking DJ-1 to neurodegeneration. Based on the findings in the rare monogenic forms of PD, the review sought to expand the knowledge on the molecular pathways involved in the common forms of PD. The review specifically focused on PARK7, an autosomal gene observed in the early onset of PD and which occurs due to mutations in DJ-1.[49] The review discussed how a dysfunction in DJ-1 might lead to neurodegeneration, and its implications for PD. A specific understanding of the role of DJ-1 was not made but its role as an oxidative sensor was consistent with current theories adopted to describe PD pathogenesis.

A study carried out by Hedrich et al.,[50] compared the rate of Dj-1(PARK7) mutations and *Parkin* (PARK2) mutations in the early-onset of PD. The study was conducted against a background of increased implication of Parkin gene and DJ-1 in the early onset of PD. The authors investigated the frequency of DJ-1 and *Parkin* gene mutations by performing a mutational analysis of coding exons using quantitative PCR assays and high performance liquid chromatography. The findings showed that DJ-1 mutations occur less frequently compared to Parkin in early-onset PD patients, however, DJ-1 mutations should be considered as a possible cause of early-onset PD.[50]

A review conducted by Ariga et al.,[51] on the neuroprotective function of DJ-1 in Parkinson's disease revealed interesting information. First, it was observed that excessive oxidation of DJ-1 renders it inactive, an occurrence observed in patients with Alzheimer's disease and sporadic PD. The finding suggested that DJ-1 plays a role in the onset and pathogenesis of sporadic Parkinsonism and familial PD.[51]

Summary

As revealed by the studies reviewed in this paper, in addition to genetics, diet and nutrition play a significant role in the development and progression of Parkinson's disease. Though the research is still ongoing regarding on the role played by a wide variety of nutrients and dietary factors, there is a clear implication of vitamin D deficiency and the intake of foods containing animal fat. Additionally, there is evidence to show that glutathione deficiency could be contributing to the development of PD, as it is the case for other degenerative conditions. The findings of the studies reviewed indicate that supplementation of vitamin D, coenzyme Q-10, glutathione precursors, coffee and black tea consumption, and consumption of other nutrients identified, could offer short term reprieve for patients suffering from PD.

Acknowledgements

None.

Conflict of interest

Author declares that there is no conflict of interest.

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