# Therapeutic Effects of Ketogenic Diet Components on Parkinson's Disease

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## Abstract:

Parkinson's disease is a neurodegenerative disease and no proper treatment or cure has been developed for it till now. Worldwide the incidence of disease has been increased with age. Latest researches have focused on the dietary aspects of Parkinson's and have revealed that a ketogenic diet may be beneficial in prevention and for therapy. The main aim of this review article was to explore the dietary elements present in ketogenic diet and their respective roles in the body with link to Parkinson's disease. Ketogenic diet has been used in many neurological diseases due to its neuroprotective effects. Ketogenic diet is a normal caloric diet that composed of with high fat (mostly composed with polyunsaturated fatty acids), medium protein and low in carbohydrates. The composition of this diet makes body to utilize fat and ketones for energy by altering glucose.

The major constituents present in a ketogenic diet which have neuroprotective effects against Parkinson's are; B complex vitamins, Omega-3 Fatty Acids, Omega-6 Fatty acids and Vitamin D. The beneficial effects have been evaluated regarding the role of constituents present in a ketogenic diet on Parkinson's disease. The need for further researches, especially clinical trials for the different constituents of ketogenic diet and their neuroprotective properties are still required.

## Key Words:

Parkinson's Disease, Ketogenic Diet, Omega-3 Fatty Acids, B-Complex Vitamins

## Introduction:

Parkinson's disease is a progressive disabling neuro-degenerative disease characterized by slow and decreased movement, muscular rigidity, resting tremor, postural instability and decreased dopamine transmission to the basal ganglia[1]. It causes memory loss with time and involuntary movements[2]. Increased caffeine intake, young age and smoking have shown to decrease the incidence of Parkinson's disease whereas the use of pesticides and an increase in the amount of dairy products has shown to increase the incidence of Parkinson's [3].

It is more common in men then in women probably because of the neuroprotective effect of estrogen[4]. Parkinson's disease is found among 0.3% of the entire population in industrialized countries. It affects 1% of the population of America and Canada over the age of 70. The incidence of disease increases with age and is rarely diagnosed before the age of 40 years[5]. About 1% of the population above 60 years of age suffers from Parkinson's[6]. The World Health Organization categorizes prevalence of Parkinson's among different regions as 0.02% in Africa, 0.22% in America, 0.30% in Europe, 0.03% in South-East-Asia, 0.06% in Eastern Mediterranean and 0.15% in Western Pacific[7]. A study conducted in South-Central India revealed that 28% of the people suffering from Parkinson's lived in urban areas, 10% came from semi-urban areas, 50% belonged to rural areas and 12% came from tribal areas [8]. According to a research conducted by Agha Khan University Pakistan, there are estimated to be 6.5 million people suffering from Parkinson's Disease worldwide out of which approximately 450,000 people are Pakistanis. The study also revealed that about a hundred new cases of Parkinson's are diagnosed every day in Pakistan [9]. Another

study conducted in Khyber Pakhtunkhwa (KPK) revealed that prevalence of Parkinson's Disease in people of KPK according to their age is 10% of age 31-40, 10% for 41-50, 23% for 51-60 and 56% for 61-80 thereby showing that incidence of Parkinson's is directly proportional to the age i.e. elder people have an increased risk of developing Parkinson's than younger people. The same study also revealed that 63.33% patients suffering from Parkinson's belonged to rural areas whereas 36.67% patients belonged to urban areas [10].

There are several elements linked to the progression and occurrence of Parkinson's disease [11]. Helicobacter pylori can be an element for the progression of Parkinson's disease[12]. Homocysteine tends to play a vital role in the progression of this disease [13]. Homocysteine is a sulphur-containing non-protein amino acid that is a naturally-occurring by-product of the S-adenosyl methionine cycle [14]. Two pathways are employed by the body to maintain Homocysteine levels within a narrow concentration range leaving sufficient Homocysteine to contribute to cellular biochemical pathways yet preventing it from building up to concentrations that can be deleterious to health. An increase in Homocysteine levels causes an increase in the neurotoxic effect on dopaminergic neurons, which in turn lead to an increase in cell death [15].

Phytoestrogens also help in prevention and progression of Parkinson's. Just like other inflammatory diseases, neuro-inflammation also produces reactive oxygen species, along with nitric oxide (NO) [16]. The more the production of these inflammatory factors, the more likely the disease is to progress[17]. Phytoestrogens like soybeans, provide estrogen which has proven to be neuroprotective in many researchers conducted against Alzheimer's disease, Parkinson's disease and Multiple Sclerosis, etc. estrogen reduces brain damage and improves the survival of neurons by inhibiting the production of pro-inflammatory molecules [18,19].

The preventive measures being studied to evaluate the role of Ketogenic Diet. Ketogenic Diet is rich in fat, adequate in proteins and low in carbohydrates. The ketone bodies produced during the metabolism of fat act as inhibitory neurotransmitters, thus causing an anticonvulsant effect on the body[20]. A number of studies have shown the neuroprotective effects of ketogenic diet in neurological disorders. One such study conducted on rats suffering from Parkinson's showed that ketogenic diet protected the dopaminergic neurons, thereby preventing Parkinson's and/or slowing down its progression[21].

## Composition of ketogenic diet and its beneficial effects:

A number of factors account for Parkinson's and diet plays a major role in it along with race, ethnicity, socioeconomic status, age and gender. Ketogenic diet has being gaining popularity with respect to Parkinson's as the diet comprises of elements that can prevent or have a therapeutic effect on Parkinson's disease [20]. Ketogenic diet is also known as Low-carb diet which is commonly used in improvement of cognitive functions in patients of Parkinson's disease[22]. It is low in carbohydrate, moderate in proteins and high in fat content. In this diet, ketones are released in the body and can be used to provide maximum fuel for energy. The diet mainly contains raw nuts, seeds, meat and poultry, low-carb vegetables, cottage cheese, plain yogurt, coconut oil and avocados. The major constituents present in this diet are Omega-3 fatty acids, Vitamin A, Vitamin D and Vitamin B complex. It improves the motor function and inhibits the progression of disease. The high-fat content and low-carb intake of ketogenic diet has anticonvulsant effect and reduces seizures[23]. Increased ketones improve the efficiency of brain, as well as, protect from neuronal death by inducing anti-inflammatory and anti-oxidants in diet[24]. The MCT-based ketogenic diet decreases the MPTP-induced neuotoxicity[25]. The various dietary elements found in Ketogenic Diet and their

impact on Parkinson's are discussed below;

## Vitamin B Complex

### Vitamin B-1:

Vitamin B-1, also known as Thiamin and found in whole-grain, fortified, or enriched grain products and is commonly known for its energy yielding role in the body i.e. it is a part of co-enzyme Thiamin Pyrophosphate (TPP) which is used in the conversion of pyruvate to acetyl Coenzyme A[26]. A deficiency in Thiamin had caused an increase in the degeneration of dopaminergic neurons as low levels of thiamin disturb the carbohydrate metabolism which in turn dysfunctions and causes selective neuronal damage. The deficiency also resulted in metabolic acidosis in the body along with inadequate energy supply to the cerebellar granule cells[27].

An experimental pilot study was conducted to evaluate the efficacy of blood serum thiamin level in relation to development of Parkinson disease. These patients who have low serum thiamin levels then enrolled in the experiments. The participants were given to the 100-200 mg per day for 5 weeks. The study results showed a positive correlation between the low serum thiamin level and the development of Parkinson's disease as well as those who received a proper thiamin dose showed the improvement in symptoms of Parkinson's disease[28].

In another study, total of 50 participants were given to 100 mg of thiamin twice a week. The results of the study showed a positive improvement in the symptoms of Parkinson's disease. The study also concluded the neuroprotective prolong effect of thiamin on Parkinson's disease[29].

### Vitamin B-6

Vitamin B-6 was also associated with brain health as it assists in the conversion of amino acid Tryptophan to Niacin and Serotonin (a neurotransmitter). It is found in meat, fish, poultry, potatoes and other starchy vegetables along with non-citrus fruits, legumes and soy products [26]. Vitamin B-6 had shown to have neuroprotective abilities as it acts as an antioxidant. Apart from the antioxidant role, Vitamin B-6 was also used in the synthesis of dopamine, a neurotransmitter which decreases the causes of Parkinson's. A study conducted in Japan revealed that a low intake of dietary Vitamin B-6 but not of Vitamin B-9, Vitamin B-12 and Vitamin B-2 increased the risk for developing Parkinson's [30].

### Vitamin B-9

Vitamin B-9 is commonly known as Folate or Folic Acid and is popular among pregnant women for its preventive roles against neural tube defects. It is present in leafy green vegetables, grains, legumes, liver and fortified cereals[26]. The increase in homocysteine levels is a risk for developing Parkinson's, folate also plays a vital role in keeping homocysteine levels balanced. Vitamin B-9 regenerates methionine, an amino acid, from homocysteine in the Methionine – Homocysteine Cycle [16]. Thereby keeping homocysteine levels low or balanced in the body. Folate also plays a role in the synthesis of different neurotransmitters like serotonin, norepinephrine and dopamine. A deficiency in Vitamin B-9 results in an increase in Homocysteine levels in the body resulting in depression along with slow-progressing neuropathy[27].

### Vitamin B-12

Vitamin B-12 is a water soluble vitamin which is widely known for its roles in new cell synthesis and maintenance of nerve cells. Its deficiency causes Pernicious Anemia in the body which is characterized by abnormally large and immature red blood cells formation. It is present in animal food sources i.e. meat, fish, poultry, seafood, milk, cheese, etc [26]. A deficiency in Vitamin B-12 has shown to result in an increase in homocysteine levels. An increase in homocysteine levels can cause the occurrence of Parkinson's in individuals. This happens because an increase in homocysteine leads to an increase in the levels of a dopaminergic

neurotoxin 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), which in turn, kill dopaminergic neurons [15]. Therefore, Vitamin B-12 prevents Parkinson's indirectly by not letting the levels of Homocysteine increase in the body.

## Omega-3-Fatty Acids

Omega-3-fatty acids are polyunsaturated fatty acids and are found in fish oils, walnuts, chia seeds and flaxseeds etc. The most common Omega-3 fatty acids are Alpha-Linolenic Acid (ALA), Docosahexaenoic Acid and Eicosapentaenoic acid (EHA). Recently a number of studies have been conducted which revealed the therapeutic effects of Omega-3 fatty acids in neurological disorders [16,26,27].

## Alpha-Linolenic Acid

Alpha-Linolenic Acid is found in flaxseed, walnut, wheat germ and canola oils along with nuts and seeds [26]. It is essential for the human body as it cannot be synthesized. Within the body, ALA is converted to DHA in the liver or in the brain. After being converted into DHA and even before that, ALA has shown to have neuroprotective effects as it reduces oxidative stress and neuro-inflammation in the body[31].

## Docosahexaenoic Acid

DHA is commonly present in fish and fish oils [26]. People suffering from Parkinson's disease are given Levodopa, a drug, which converts into Dopamine in the body. Saturated fatty acids hinder this process whereas research has shown that polyunsaturated fatty acids like DHA, aid in the process and further act as a preventive agent against neuro-inflammation. It also binds with reactive oxygen species and decreases the oxidative stress on the body, especially in the brain[32].

## Eicosapentaenoic Acid

EPA are also found commonly in fish and fish oils [26]. The concentration of EPA in the brain is relatively low as it is catabolized fairly rapidly by β- oxidation. People who consume a diet rich in Omega-3 fatty acids, especially EPA, have a very low chance of developing depression or dementia. Furthermore, a study on children revealed that those whose diet was deficient in Omega-3 fatty acids were more likely to suffer from less cognitive defects[33].

## Vitamin D

Vitamin D is a fat soluble vitamin which is essential for bone health. It is synthesized in the body due to sunlight. Among food sources, it is present in liver, fatty fish and their oils, egg yolks, margarine, butter, beef and fortified milk and juices [26]. Studies have showed that people who had a higher level of serum Vitamin D were at a reduced risk of developing Parkinson's Disease than those who did not[34]. Another study conducted in Japan revealed that people with Parkinson's Disease patients had a lower serum Vitamin D level than normal people[35]. Vitamin D also plays a neuroprotective effect in the body due to its anti-inflammatory properties [36]. Apart from that, it is also used to regulate the expression of glial cell line-derived neurotrophic factor (GDNF), whose administration has been shown to alleviate the symptoms of Parkinson's Disease [37]. Another role that Vitamin D plays is maintaining the homeostasis of calcium in the blood. An increase in calcium levels can lead to the death of dopaminergic neurons, in turn putting the person at an increased risk of developing Parkinson's[38].

## Vitamin E

Vitamin E is famously known for its role as an antioxidant in the human body. It is also a fat soluble vitamin and is found in wheat germ, whole grains, liver, egg yolks, nuts, seeds, fatty meats and green leafy vegetables like spinach 26. It has eight derivatives out of which α-Tocopherol is the most important when it comes to the human body. A study revealed that apart from antioxidant properties of Vitamin E, it also exhibited other non-oxidative cytoprotective effects which may be beneficial in preventing Parkinson's [39]. However, further work needs to be done in order to fully understand the preventive and therapeutic effects of Vitamin E against Parkinson's as there is no real promising

study or clinical trial which supports this notion.

## Calcium

Calcium is a mineral which is found in dairy products and is essential for bone health [26]. However, that's not just where Calcium's role in the body stops. It is present in the axon and guards the gateway through which a nerve impulse travels from an axon of one neuron to the dendrite of another neuron[40]. Glutamate is an excitatory neurotransmitter and when it crosses the synapse it activates α-amino-3-hydroxy-5-methylisoxazole-4-propionate acid (AMPA) and N-methyl-d-aspartate (NMDA) receptor channels which in turn increase the concentration of cytoplasmic Ca2+ and in doing so, it indirectly activates the voltage dependent Ca2+ channels. This causes damage to the neurons and ultimately leads to neuronal cell death, therefore high levels of calcium are not advised for people suffering from Parkinson's [41].

## Potassium

Potassium is another mineral which is involved in the nerve impulse transmission. It is found in meats, milks, fruits, vegetables, grains and legumes [26]. Potassium channels in neurons are highly sensitive to ATP molecules and protect against neurotoxicity caused by insecticides like rotenone, therefore showing that Potassium may have even more beneficial effects against neurotoxicity and cell death and more researches should be conducted to understand its benefits to the fullest[42].

| Ketogenic Diet | Subjects | Duration | Neuroprotective Effect | References |
|---|---|---|---|---|
| High in fat (essential fatty acids) 35%, low in protein, Moderate in carbohydrates | 11 | 8 weeks | Reduction in Parkinson's disease symptoms | Branco AF *et al.*,[23] |
| High fat, low in protein, moderate in Carbs | 16 | 28-days exposure | 43% reduction in Parkinson's disease symptoms | Vanitallie TB *et al.*,[25] |
| Diet highly enriched in Omega-3 and Omega-6 fatty acids | 23 | 50 days | Anti-oxidant and anti-inflammatory effects help to reduce dopaminergic damage | Mori MA *et al.*,[31] |
| Highly enriched with Vitamin D3, Low in carbohydrates 31% | 114 | 12 months | Produced neuroprotective effect | Suzuki M *et al.*,[35] |
| Highly enriched with Vitamin D3, potassium and vitamin E | 93 | 4 weeks | Improvement in cognitive functions and reduce oxidative stress | Bazinet RP *et al.*,[33] |

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|---|---|---|---|---|
| Diet enriched with Alpha-Linolenic Acid | 32 | 4 weeks | Anti-oxidant property help to | Zhang H *et al.*,[43] |
| Diet enriched with unsaturated fatty acids | 51 | 3 weeks | Reduction in Parkinson's disease symptoms | De Lau *et al.*,[44] |

**Table 1:** Summary of the effects of Ketogenic Diet Components on Parkinson's disease

## Conclusions:

Ketogenic Diet has its beneficial and therapeutic effects on Parkinson's disease but at the same time however, some components of this diet may in fact promote Parkinson's. Therefore, nutrients which may promote Parkinson's should be avoided while planning a Ketogenic Diet to ensure its complete beneficial effects to sustain brain health.

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