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The Effect of the Ketogenic Diet on the Therapy of Neurodegenerative Diseases and Its Impact on Improving Cognitive Functions

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Abstract
The ketogenic diet (KD) is a high-fat and low-carbohydrate diet with controlled amounts of protein. The use of drastic caloric restriction or ultralow-carbohydrate diets increases the production of ketone bodies, which are an alternative energy substrate in situations of insufficient glucose supply. Alzheimer's disease (AD) and Parkinson's disease are the most common neurodegenerative diseases in the world. It is believed that carbohydrate metabolism disorders may affect the progression of these diseases, as confirmed by both animal and human studies. Among patients with AD, the presence of ketone bodies in the body can improve cerebral circulation. Among Parkinson's patients, the presence of ketone bodies can reduce muscle tremor and stiffness, as well as improve cognitive function. The results of the research indicate that using a low-carbohydrate diet, including a KD, may have a beneficial effect on brain function in diseases that cause neuronal damage.

Introduction

The ketogenic diet (KD) is a high-fat, low-carbohydrate diet with controlled amounts of protein. The proportion of carbohydrates in the food ration is less than 10%. Such a low supply of sugars causes fatty acids to be converted to ketone bodies and used as the main energy substrate when glucose, the brain's energy source, is in short supply. Different models of the KD are currently used, depending on the goal of therapy. What is particularly noteworthy is its importance in the treatment of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD) [1–3]. This study aims to evaluate the validity of the KD among people with AD and PD, and its effect on improving cognitive function.

Review

Ketosis

During calorific restriction or extremely low-carbohydrate diets, insulin production by pancreatic β-cells is reduced, lipogenesis is decreased and glycogen stores are depleted. When glycogen stores are too low, it is necessary to obtain an alternative substrate to provide sufficient energy for central nervous system function and fat oxidation, in order to carry out energy processes. Fatty

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acids produce acetoacetate, which is converted to acetone and beta-hydroxybutyrate (BOHB). Ketones are then detected in the urine (ketonuria), in the blood (ketonaemia) and in the exhaled air. Ketosis is indicated by reaching a blood BOHB concentration of ≥0.5 mmol/L. Ketone bodies are used in tissues, serving as their main energy substrate. In the state of ketosis, blood glucose levels are stable, reaching physiological values. Apart from the small amount supplied by the diet, glucose is then produced by gluconeogenesis from amino acids and by oxidation of fatty acids. Nutritional ketosis can be achieved by following a KD or fasting [2, 4]. The products of ketone body metabolism can cover as much as 80% of the brain's energy needs, while also showing neuroprotective effects, which are especially important in neurological disorders. For the remaining 20% of the area, glucose is the sole source of energy [5, 6].

The Ketogenic Diet

The classic KD is characterized by a 4:1 ratio of fats to carbohydrates and proteins, where for every 4 g of fats, there is 1 g of carbohydrates and proteins combined. Various modifications of the classic KD are currently in use. It is assumed that in a KD about 70%–80% of energy should come from fat, and the rest of the requirement should be covered by proteins and carbohydrates. The amount of carbohydrates must not exceed 50 g/day. Once the adaptation to using ketone bodies as the main energy substrate has taken place, these ratios are modified. Attention is paid not only to macronutrient ratios but also to vitamins and minerals. The classic KD is generally a low-energy diet [2].

Another variation of the KD is the *Modified Atkins Diet*. It is a less restrictive form of the classic KD. It carries a lower risk of side effects than classical KD [7].

Alzheimer's Disease

AD is the most common cause of dementia worldwide. It is estimated to affect more than 35 million people. It is a progressive condition manifested by cognitive decline [8, 9]. The disease is characterized by abnormalities at the molecular and biochemical levels. The condition also involves an impairment of energy production at the mitochondrial level, the formation of large amounts of free radicals and DNA damage. These changes are progressive and lead to irreversible neuronal destruction, resulting in death of the patient [10, 11].

The cause of the disease is currently unknown, but several factors have been identified that may predispose to its occurrence. The most important of these is the aging of the body and the occurrence of type 2 diabetes [10, 11]. One's genetic makeup is another factor that promotes the development of AD [9, 12].

Disorders of Glucose Metabolism: A Predisposing Factor for AD

In AD, glucose metabolism is impaired at the nerve cell level. There is an association between the occurrence of type 2 diabetes and the progression of neurodegenerative processes. Increased risk of AD correlates with hyperinsulinemia, a component of insulin resistance. Insulin receptors are located in areas of the brain that are particularly vulnerable to neurodegeneration. However, insulin must be delivered to them with blood because it is not synthesized in sufficient amounts in the brain. This hormone plays a significant role in the regulation of pro-inflammatory cytokines and the formation of neuroplastic and neurotrophic factors, which are essential for memory processes and the disposal of amyloid beta from the brain. Insulin deficiency in the brain leads to dysregulation of these mechanisms [13, 14].

Effects of Ketonaemia and KD on the Course of AD

In people with AD, damage to the mechanisms that allow glucose to be used in energy processes is observed. Reducing its supply in favor of a substrate that can be used more efficiently by the brain appears to be a reasonable addition to therapy. Reducing carbohydrate supply during KD results in a decrease in insulin levels, which stimulates the oxidation of fatty acids to ketone bodies, which then permeate the blood. BOHB and acetoacetate cross the blood-brain barrier. The ability to utilize ketone bodies in individuals with AD is preserved, allowing the brain to efficiently carry out energy processes using them [11].

The presence of ketone bodies in blood has a beneficial effect in AD. Ketone bodies reduce β-amyloid, improve mitochondrial function, and reduce reactive oxygen forms in the hippocampus [11].

Krikorian et al. [14] conducted a study involving 5 individuals over 70 years of age, with diagnosed mild cognitive impairment (MCI), aiming to demonstrate that a KD can improve memory. The study group was examined for brain biochemical composition using proton magnetic resonance spectroscopy (H MRS). Patients were also tested for cognitive functions such as long- and short-term memory and mood stability. In this group, a dietary intervention was introduced to reduce dietary carbohydrates to 20–50 g/day. After a few hours of carbohydrate restriction, the process of adaptation to ketosis begins and takes about 3 weeks. Dietary protein and fat supply were

not restricted. At the end of the 6-week dietary intervention, an increase in serum BOHB levels, a reduction in waist circumference and weight of the subjects was observed, with a slight decrease in glucose and insulin levels. Changes in the biochemical composition of the brain resulted in improved memory – both short- and long-term – but there was no effect of dietary intake on the mood of study participants [14].

In another study conducted by Taylor et al. [11], 10 patients diagnosed with a mild form of Alzheimer's underwent a dietary intervention to introduce a KD containing 70% fat for 3 months. In the first part of the study, 10% of the required energy from fat was supplied by MCT oil. Its amount was gradually increased until it reached 40% of energy from fat. When analyzing the results of the study, no significant differences were observed in biochemical parameters after the diet, but better results were reported in tests measuring the patients' ability to remember and focus attention [11].

The study authors suggest that diets that induce a state of ketosis may improve memory and other cognitive functions. The benefits of carbohydrate restriction (20–50 g/day) and the addition of MCT have been reported after only 6 weeks on the diet [11, 14].

Benefits of Ketone Bodies in the Blood in Patients with AD

A study conducted by Ota et al. [15] demonstrated that consumption of MCT oil as a supplement to the usual diet raises the blood levels of ketone bodies and affects cognitive function in AD patients. A group of people over the age of 70 years with diagnosed early- or intermediate-stage AD was selected. A formulation containing 50 g of MCT was administered to the subjects for 12 weeks. There was no difference in test scores after a single intake of an MCT-containing formula, but subjects consuming medium-chain triglycerides for 12 weeks displayed significantly better scores on the Trail Making Test, the Wechsler Adult Intelligence Scale III test, and the Wechsler Memory Scale – revised method tests compared to the control group. The effects of ketone bodies were seen even when serum BOHB concentrations dropped to <0.5 mmol/L. The authors of the study concluded that one does not have to be continuously in nutritional ketosis to derive health benefits from the intermittent presence of ketone bodies in serum [15].

Other studies also indicate that it is possible to achieve improvements in cognitive function in AD patients despite the absence of a deep ketosis state. The use of caprylic acid alone (which is part of medium-chain triglycerides) at approx. 20 g for approx. 3 months resulted in an increase in serum BOHB levels to <0.4 mmol/L, which may have a therapeutic effect in some individuals, although entry into the ketosis state is indicated by BOHB levels at >0.5 mmol/L [2, 8].

Medium-chain triglycerides pass through the blood-brain barrier. The brain metabolizes them in a different way than ketone bodies. Caprylic acid ester is metabolized by astrocytes, affecting memory and learning processes, which may improve synapse function in the hypoglycemic state. Ketone bodies are oxidized by both neurons and astrocytes [16].

Parkinson's Disease

Like AD, PD is one of the most common neurodegenerative diseases in the world. It affects more than 1% of the population over 60 years of age [16]. It is a chronic, progressive disease associated with destruction of dopaminergic neurons and progressive loss of mobility and cognitive impairment. The causes of the disease remain unknown, but a multifactorial pathogenesis, including mitochondrial dysfunction, abnormal glucose metabolism in the brain, or inflammation within the nervous system, is indicated [17, 18].

Movement disorders associated with PD include hypokinesia, muscle stiffness, tremors, and difficulty maintaining normal posture. Extramotor symptoms worsen the quality of life of patients with PD. These include mood disorders, memory problems, pain, sleep problems, and impairment of the autonomic nervous system. People with PD also suffer from depression, impaired sense of smell and taste, and constipation [19]. The onset of PD dementia worsens the patient's prognosis [20, 21].

Cognitive impairment is an early sign of the disease. MCI is diagnosed in 20%–33% of people with newly diagnosed disease. Furthermore, 60%–80% of patients with PD and MCI develop dementia over the next 12 years [22].

It is estimated that 50%–80% of PD patients are simultaneously diagnosed with impaired carbohydrate metabolism. Peripheral tissue insulin resistance is often the first symptom of PD and is associated with abnormal energy metabolism within the brain [23]. Current forms of therapy (e.g., the use of L-DOPA) can prevent the onset of motor dysfunction but do not affect other cognitive functions [24].

KD in PD

According to the position of an interdisciplinary board of experts, a protein redistribution diet is recommended

for patients with PD. It involves limiting protein intake in the morning and afternoon to optimize absorption of L-DOPA, the most effective drug used to treat PD. High-protein foods should be consumed in the evening [25]. High-carbohydrate and low-fat diets may facilitate the conversion of tyrosine to dopamine, a deficit of which is observed in PD. In addition, a high intake of dietary fiber results in increased production of short-chain fatty acids in the intestine through the endogenous gut microbiota, which also benefits the nervous system, including intestinal motility [24].

It is also believed that PD patients have defects in the function of respiratory chain complex I, which is involved in the production of energy from glucose. Ketone bodies mainly pass through respiratory complex II, so they may serve as a more efficient energy substrate than glucose, enabling proper mitochondrial function and energy production in the brain. Therefore, the KD may prove to be a beneficial option in patients with PD. Putting the patient into a state of ketosis affects both their motor functions, i.e., hypokinesia, muscle tremors, or stiffness, as well as non-motor impairments such as impaired memory and cognitive function [24].

A study conducted by Shaafi et al. [17], examined the effects of a KD on a group of 56 rats with an animal model of PD. It was observed that limiting glucose supply enhances the resistance of neurons in the substantia nigra to destruction and prevents the progression of PD symptoms. The animals were divided into groups: a control group, a placebo group, a healthy group on the KD, sick animals on a regular diet, sick animals on the KD, sick animals taking pramipexole on a regular diet, and sick animals taking pramipexole and being on the KD. To induce a state of ketosis, a selected group of rats was fed a diet, including MCT oil for a period of 24 days, covering 50% of their daily energy requirements. After 2 weeks, serum BOHB levels increased. The rats were examined to check the degree of catalepsy. An analysis of the study results showed no differences between the control and placebo groups. The largest differences were observed among animals on KD. The authors concluded that administering the KD slightly increases the effect of pramipexole on motor function [17].

Side Effects of the KD

Keto-Adaptation and the "Keto-Flu" Phenomenon

When inducing a state of ketosis, a number of side effects can occur due to changes in metabolic levels, which appear a few days after the diet is first introduced. The phenomenon is commonly referred to as "*keto flu*" and passes spontaneously after a few days. The timing of adverse reactions is individual [2]. The most commonly cited side effects include nervous system disorders such as trouble concentrating, as well as muscle pain, feelings of weakness and lack of energy, and bloating or constipation [2].

Side effects of MCTs can include gastrointestinal ailments, such as diarrhea or abdominal pain – which, like the other symptoms, pass after a few days. The addition of MCT oil to the diet accelerates the efficient use of ketone bodies by the body, so that the discomfort associated with keto-adaptation lasts shorter [2].

Side Effects of Long-Term Use of the KD

The authors of an animal model study suggest that following a KD may lower bone mineral density (BMD). In a study conducted by Xu et al. [3], rats were divided into three groups: one was fed standard feed for laboratory animals, the second received a classic 3:1 KD, and the third group alternated between 1 day of classic KD and 1 day of fasting (*every – other – day ketogenic diet, EODKD*). The animals were fed this way for 12 weeks. After this time, their body weight, body fat, and *BMD were controlled.* Rats fed the KD were characterized by the presence of a reduced mass of both cortical bone and sin cancellous bone in hind limb bones. The occurrence of lower mechanical strength of the harvested bones was also observed. Researchers have suggested that osteoblasts are inhibited and osteoclasts are stimulated when KD and EODKD are used. Higher body mass in the test animals had a protective effect on preserving bone mass, although excessive weight and obesity were associated with more fractures and reduced BMD. Serum calcium, phosphorus, and vitamin D concentrations did not differ among the three study groups, suggesting that dietary vitamin and mineral content when on the KD is not protective against osteoporosis risk. Ding et al. [26] further demonstrated that these lesions mainly affect the bones of the extremities and, to a lesser extent, the bones of the head and trunk.

Studies involving humans are inconclusive on this issue. In a study by Bertoli et al. [27] involving three women following a KD for 5 years, no negative effect of this diet on the subjects' skeletal status was observed. The authors suggested that the effect of KD on BMD may be age-related, with more changes seen in children whose skeleton is not yet mature. In adults with a formed bone, this diet presents no such effect. The effect of long-term KD use on BMD in humans requires further study.

In a study conducted by Phillips et al. [28], 26 patients switched to KD for 12 weeks. The diet contained 58%E from fats (including 26%E from saturated fatty acids and 32%E from unsaturated fatty acids), 29%E from protein, 7%E from fiber, and 6%E from assimilable carbohydrates. Side effects that have been observed among AD patients include, among others, high nervousness, fatigue, muscle cramps, constipation, and an increased desire to eat sugary foods. These occurred both after 6 weeks from the intervention and on the day the intervention ended [28].

Use of KD by Seniors: Risks

Among the elderly, malnutrition is a particularly common problem, caused by comorbidities, poor nutrition, and the aging process. Patients with dementia are more likely to develop it than healthy individuals [29]. Malnutrition is associated with an inadequate and/or insufficient supply of nutrients, which can affect the loss of muscle mass and also contribute to poorer health, including the potential for premature death [30].

People diagnosed with PD are more likely to be malnourished and have a lower BMI compared to healthy individuals. The cause of this phenomenon is not fully understood. This is believed to be influenced by factors such as the severity of the condition, the presence of seizures, dyskinesia, and limited food intake among PD patients. Some patients are diagnosed with taste and smell disorders that may be related to dietary changes [31].

People suffering from AD are significantly more likely to develop sarcopenia compared to healthy individuals. The use of classic 4:1 and 3:1 KDs may exacerbate malnutrition and loss of muscle mass due to the reduced calorific value of the diet and low protein supply [2, 32]. The authors of some studies suggest that KD can prevent muscle atrophy, but other studies do not support this [33, 34].

Following low-carbohydrate diets often leads to reduced appetite and suppressed hunger. Seniors, especially those with dementia, suffer from a number of food intake disorders, including lack of appetite and swallowing problems. The use of KD in patients with preexisting abnormalities may result in skipping meals and thus lead to energy and nutrient deficiencies, which will result in worsening of the patient's condition [35]. In the senior population, the elimination of certain foods (so-called food "pickiness") is observed, which can increase the risk of malnutrition. A study involving 559 people over the age of 65 examined the effects of food selectivity on nutritional status. Difficulties that may have been experienced in consuming particular products were also considered, i.e., missing teeth, problems with grinding, swallowing, and ingesting a bite of food. It was observed that greater food pickiness was strongly correlated with an increased risk of malnutrition compared to those consuming more foods [30].

Constipation is frequently diagnosed among patients with PD and AD. The KD is characterized by low-carbohydrate supply and therefore, it is low in dietary fiber. Especially in the first few weeks of its use, constipation problems may become worse. No studies are currently available to assess the long-term effects of low-carbohydrate diets on gut microbiota and gut health [2, 32].

In addition to impaired concentration, muscle pain, subjective feelings of lack of energy and weakness, and bloating and constipation, the occurrence of nausea, vomiting, hypoglycemia, hypercalciuria, hypocalcemia, and hypertriglyceridemia are among the early side effects of implementing the KD. The consequences of dehydration can be particularly dangerous, especially for representatives of the senior population [36].

The effects of long-term KD use include those occurring during the induction of a state of ketosis, as well as the more serious side effects: the presence of protein in urine, hyperuricemia, and metabolic acidosis, especially with coexisting diabetes and inadequate insulin dosage. Increased aminotransferase activity is also observed. When following a KD, the risk of urinary tract lithiasis also increases. Most discomfort passes spontaneously after the first few weeks of the diet, but the risk of more severe complications can be a significant problem in the senior population, burdened with a large number of conditions resulting from aging [36].

Conclusion

Low-carbohydrate diets are claimed to have beneficial effects on brain function. A switch to KD is recommended both in the treatment of neurodegenerative diseases and to improve memory and learning efficiency among healthy individuals [15]. Authors of studies on the effects of the KD on improving cognitive function in people with AD or PD point to its positive effects on neuronal function. This prevents the progression of neurodegeneration, which significantly improves the patient's quality of life [10, 11, 13, 17, 18, 23]. The risks associated with adverse effects of the diet prevent the KD from being recommended for routine use among individuals with AD and PD [2, 36–38]. The KD may support the treatment of neurodegenerative diseases, but further studies involving larger numbers of patients are required to recommend it

as a preventive measure among those at high risk for these conditions. There are also no long-term studies that can confirm that following a KD can inhibit the development of dementia in Alzheimer's or Parkinson's patients without causing harmful side effects. Particular attention should be paid to the risk of malnutrition in this group of patients. Also, the selectivity of food choices may exacerbate it [29, 30]. It is necessary to develop a management protocol that is safe for this group of patients and leads to the desired therapeutic effect, eliminating possible side effects [15]. In light of recent reports, it seems more reasonable to use MCT oil and BOHB-containing supplements in addition to the standard diet than to follow a KD among AD and PD patients [2, 8, 15, 16].

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conception and design: Klaudia Grochowska; drafting of manuscript: Klaudia Grochowska and Anna Przeliorz; and critical revising the manuscript: Anna Przeliorz.

References

1 Tylor MK, Swierdlow RH, Burns JM, Sullivan DK. An experimental ketogenic diet for Alzheimer disease was nutritionally dense and rich in vegetables and avocado. Curr Dev Nutr. 2019 Feb 20;3(4):nzz003.

2 Harvey C, Schofield GM, Williden M, McQuillan JA. The effect of medium chain triglycerides on time to nutritional ketosis and symptoms of keto-induction in healthy adults: a randomised controlled clinical trial. J Nutr Metab. 2018 May 22;2018:2630565.

3 Xu X, Ding J, Wu X, Huang Z, Kong G, Liu Q, et al. Bone microstructure and metabolism changes under the combined intervention of ketogenic diet with intermittent fasting: an in vivo study of rats. Exp Anim. 2019 Apr 3;68(3):371–80.

4 Stubbs BJ, Cox PJ, Evans RD, Santer P, Miller JJ, Faull OK, et al. On the metabolism of exogenous ketones in humans. Front Physiol. 2017 Oct 30;8:848.

5 St-Pierre V, Vandenberghe C, Lowry CM, Fortier M, Castellano CA, Wagner R, et al. Plasma ketone and medium chain fatty acid response in humans consuming different medium chain triglycerides during a metabolic study day. Front Nutr. 2019 Apr 16;6:46.

6 Svart M, Gormsen LC, Hansen J, Zeidler D, Gejl M, Vang K, et al. Regional cerebral effects of ketone body infusion with 3-hydroxybutyrate in humans: reduced glucose uptake, unchanged oxygen consumption and increased blood flow by positron emission tomography. A randomized, controlled trial. PLoS One. 2018 Feb 28;13(2):e0190556.

7 Poorshiri B, Barzegar M, Tahmasebi S, Shiva S, Raeisi S, Ebadi Z. The efficacy comparison of classic ketogenic diet and modified atkins diet in children with refractory epilepsy: a clinical trial. Acta Neurol Belg. 2019;5(1):60–3.

8 Farah BA. Effects of caprylic triglyceride on cognitive performance and cerebral glucose metabolism in mild Alzheimer's disease: a single-case observation. Front Aging Neurosci. 2014 Jul 16;6:133.

9 Wu L, Zhang X, Zhao L. Human ApoE isoforms differentially modulate brain glucose and ketone body metabolism: implications for Alzheimer's disease risk reduction and early intervention. J Neurosci. 2018 Jul 25;38(30):6665–81.

10 Caberlotto L, Nguyen T, Lauria M, Priami C, Rimondini R, Maioli S, et al. Cross-disease analysis of Alzheimer's disease and type-2 diabetes highlights the role of autophagy in the pathophysiology of two highly comorbid diseases. Sci Rep. 2019 Mar 8;9:3965.

11 Taylor MK, Sullivan DK, Mahnken JD, Burns JM, Swerdlow RH. Feasibility and efficacy data from a ketogenic diet intervention in Alzheimer's disease. Alzheimers Dement. 2017 Dec 6;4:28.

12 Henderson ST, Poirier J. Pharmacogenetic analysis of the effects of polymorphisms in APOE, IDE and IL1B on a ketone body based therapeutic on cognition in mild to moderate Alzheimer's disease; a randomized, double-blind, placebo-controlled study. BMC Med Genet. 2011 Oct 12;12:137.

13 Krikorian R, Shidler MD, Dangelo K, Couch SC, Benoit SC, Clegg DJ. Dietary ketosis enhances memory in mild cognitive impairment. Neurobiol Aging. 2012;33(2):425–7.

14 Krikorian R, Boespflug EL, Dudley JA, Norris MM, Chu WJ, Summer SS, et al. Enhanced cerebral bioenergetics with dietary ketosis in mild cognitive impairment. Nutr Aging. 2014 Jan;1:223–32.

15 Ota M, Matsuo J, Ishida I, Takano H, Yakoi Y, Hori H, et al. Effects of a medium-chain triglyceride-based ketogenic formula on cognitive function in patients with mild-to-moderate Alzheimer's disease. Neurosci Lett. 2019 Oct 24;690:232–6.

16 Page KA, Williamson A, Yu N, McNay EC, Dzuira J, McCrimmon RJ, et al. Medium-chain fatty acids improve cognitive function in intensively treated type 1 diabetic patients and support in vitro synaptic transmission during acute hypoglycemia. Diabetes. 2009 May;58(5):1237–44.

17 Shaafi S, Najmi S, Aliasgharpour H, Mahmoudi J, Sadigh-Etemad S, Farhoudi M, et al. The efficacy of the ketogenic diet on motor functions in Parkinson's disease: a rat model. Iran J Neurol. 2016 Apr 3;15(2):63–9.

18 Evans JR, Mason SL, Williams-Gray CH, Foltynie T, Brayne C, Robbins TW, et al. The natural history of treated Parkinson's disease in an incident, community based cohort. J Neurol Neurosurg Psychiatry. 2011 Oct;82(10):1112–8.

19 Politis M, Wu K, Molloy S, Bain PG, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. Mov Disord. 2010 Aug 15;25(11):1646–51.

20 Aarsland D, Andersen K, Larsen JP, Lolk A, Nielsen H, Kragh-Sørensen P. Risk of dementia in Parkinson's disease: a community-based, prospective study. Neurology. 2001 Mar 25;56(6):730–6.

21 Santiago JA, Potashkin JA. Integrative network analysis unveils convergent molecular pathways in Parkinson's disease and diabetes. PLoS One. 2013 Dec 20;8(12):e83940.

22 Roheger M, Kalbe E, Liepelt-Scarfone I. Progression of cognitive decline in Parkinson's disease. J Parkinsons Dis. 2018;8(2):183–93.

23 Krikorian R, Shidler M, Summer S, Sullivan PG, Duker AP, Isaacson RS, et al. Nutritional ketosis for mild cognitive impairment in Parkinson's disease: a controlled pilot trial. Clin Park Relat Disord. 2019 Aug 6;1:41–7.

24 Phillips MCL, Murtagh DKJ, Gilbertson LJ, Asztely FJS, Lynch CDP. Low-fat versus ketogenic diet in Parkinson's disease: a pilot randomized controlled trial. Mov Disord. 2018;33(8):1306–14.

25 Karbowniczek A, Sienkiewicz-Jarosz H, Czernuszenko A, Kłęk S, Sobów T, Sławek J. Leczenie żywieniowe w neurologii – stanowisko interdyscyplinarnej grupy ekspertów. Część II. Rola żywienia w chorobie Parkinsona. Pol Przegl Neurol. 2018;14(3):117–30.
26 Ding J, Xu X, Wu X, Huang Z, Kong G, Liu J, et al. Bone loss and biomechanical reduction of appendicular and axial bones under ketogenic diet in rats. Exp Ther Med. 2019 Apr; 17(4):2503–10.
27 Bertoli S, Trentani C, Ferraris C, De Giorgis V, Veggiotti P, Tagliabue A. Long-term effects of a ketogenic diet on body composition and bone mineralization in GLUT-1 deficiency syndrome: a case series. Nutrition. 2014; 30(6):726–8.
28 Phillips MCL, Deprez LM, Mortimer GMN, Murtagh DKJ, McCoy S, Mylchreest R, et al. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. Alzheimers Res Ther. 2021 Feb 23;13(1):51.
29 Krzyminska-Siemaszko R, Chudek J, Suwalska A, Lewandowicz M, Mossakowska M, Kroll-Balcerzak R, et al. Health status correlates of malnutrition in the polish elderly population: results of the Polsenior study. Eur Rev Med Pharmacol Sci. 2016 Nov;20(21):4565–73.
30 Maitre I, Van Wymelbeke V, Amand M, Vigneau E, Issanchou S, Sulmont-Rossé . Food pickiness in the elderly: relationship with dependency and malnutrition. Food Qual Prefer. 2014;32(Pt B):145–51.
31 Roos DS, Oranje OJM, Freriksen AFD, Berendse HW, Boesveldt S. Flavor perception and the risk of malnutrition in patients with Parkinson's disease. J Neural Transm. 2018; 125(6):925–30.
32 Ogawa Y, Kaneko Y, Sato T, Shimizu S, Kanetaka H, Hanyu H. Sarcopenia and muscle functions at various stages of Alzheimer disease. Front Neurol. 2018 Aug 28;9:710.
33 Klement RJ, Sweeney RA. Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. BMC Res Notes. 2016;9:143.
34 Nakao R, Abe T, Yamamoto S, Oishi K. Ketogenic diet induces skeletal muscle atrophy via reducing muscle protein synthesis and possibly activating proteolysis in mice. Sci Rep. 2019 Dec 23;9:19652.
35 Gibson AA, Seimon RV, Lee CMY, Franklin AJ, Markovic TP, Caterson ID, et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. Obes Rev. 2014 Jan;16:64–76.
36 Herrero JR, Villarroya EC, Peñas JJG, Alcolea BG, Fernández BG, Macfarland LAP, et al. Safety and effectiveness of the prolonged treatment of children with a ketogenic diet. Nutrients. 2020 Jan 24;12(2):306.
37 Gyorkos A, Baker MH, Miutz LN, Lown DA, Jones MA, Houghton-Rahrig LD. Carbohydrate-restricted diet and exercise increase brain-derived neurotrophic factor and cognitive function: a randomized crossover trial. Cureus. 2019 Sep 9;11(9):e5604.
38 Marosi K, Kim SW, Moehl K, Scheibye-Knudsen M, Cheng A, Cutler R, et al. 3-Hydroxybutyrate regulates energy metabolism and induces BDNF expression in cerebral cortical neurons. J Neurochem. 2016 Dec; 139(5):769–81.