REVIEW ARTICLE

CONTENTS

Exploring the Neurological Impacts of the Ketogenic Diet: A Comprehensive Review

Piotr Kucharczyk, Kinga Szczepanik, Karolina Parzęcka, Anna Żerańska, Mateusz Michalak, Bartłomiej Kusy, Olaf Domaradzki , Wojciech Bieńkowski, Julia Charkot
MEDICAL UNIVERSITY OF WARSAW, WARSAW, POLAND

ABSTRACT

Aim: This review aims to conduct an analysis of potential therapeutic effects, mechanisms of action, and consequences of the ketogenic diet in the context of the mentioned neurological disorders.

Materials and Methods: A review of scientific literature available in the PubMed and Google Scholar databases was conducted, utilizing key terms.

Conclusions: The presented work provides an integrated compilation of currently available studies analyzing the impact of the ketogenic diet and underscores the importance of continuing research to achieve a fuller understanding of the mechanisms of action of this diet and its potential therapeutic benefits.

KEY WORDS: Ketogenic diet, neurological disorders, epilepsy, Alzheimer's disease, migraine, depression, Parkinson's disease

Wiad Lek. 2025;78(8):1664-1669. doi: 10.36740/WLek/208442 DOI

INTRODUCTION

In the human body, the main energy source is glucose. After a meal is consumed, glucose goes through numerous chemical processes. Part of the ingested carbohydrate is used as an energy substrate, part is stored as glycogen in the liver and muscles, part is converted to fat and stored as adipose tissue. Glycogen acts as an energy reserve and is converted back into glucose when needed. When glycogen stores are depleted and the body is unable to cover the resulting energy gap, it begins to produce glucose on its own from protein (through the breakdown of its own muscles), fats and lactate (which is formed during the anaerobic burning of glucose in the muscles). After a few days of the starvation period, the body adapts and ketones become the main source of energy.

Therapy based on dietary restrictions dates back to the time of Hippocrates, when fasting was the only known treatment for epilepsy. Also in the Bible, passages can be found where a boy is cured of epileptic seizures by means of 'prayer and fasting'. The first modern description of fasting as a treatment method appears in 1911, when a pair of French doctors, Guelpa and Marie, undertook the treatment of 20 children and adults, suffering from epilepsy, with food restriction and documented a milder course of epileptic seizures. In the early 1920s, Drs Cobb and Lennox of Harvard Medical School also began to study the effect of starvation on epileptic seizures. They were the first to discover that epileptic seizures were relieved about 3-4 days after the introduction of food restriction [1]. However, it was in 1921 that two key observations were made. Dr Rollin Woodyatt observed that acetone and beta-hydroxybutyric acid appear in a healthy patient not only as a result of starvation, but can also occur as a result of a diet containing too little carbohydrate and/or too much fat [1]. At the same time, Dr Russell Wilder described that the therapeutic benefits of introducing fasting can also be achieved by other means – the so-called 'ketogenic diet'.

AIM

This review aims to conduct an analysis of potential therapeutic effects, mechanisms of action, and consequences of the ketogenic diet in the context of the mentioned neurological disorders.

MATERIALS AND METHODS

A review of scientific literature available in the PubMed and Google Scholar databases was conducted, utilizing key terms.

REVIEW AND DISCUSSION

THE KETOGENIC DIET, THE ROLE OF KETONES

The oxidation of ketone bodies becomes an important factor affecting the overall energy metabolism of humans in numerous physiological states, such as fasting, starvation, the post-exercise state, pregnancy, the neonatal period, or just the use of low-carbohydrate diets [2]. The classic ketogenic diet is characterised by a high dietary fat content, the reduction of carbohydrate intake to the minimum necessary and the consumption of an adequate amount of protein. The aim of the ketogenic diet is to induce a state of ketosis in the body, which is characterised by increased lipolysis (breakdown of fatty acids) and ketogenesis, i.e. precisely the formation of ketone bodies. During a ketogenic diet, as with starvation, there is an increased production of ketone bodies (i.e. β-hydroxybutyrate), acetoacetate and acetone [3]. Studies show that ketone bodies not only function as energy fuel for tissues such as the brain, heart and skeletal muscle, but also play an important role as mediators or catalysts of various chemical processes in the body [2]. The brain is the most energy-intensive organ in the human body, for which the main source of energy is glucose. However, when the need arises, this main energy source can also be provided by ketone bodies, which can meet up to 60% of the brain's energy requirements [4].

With an increasing number of studies dedicated to the effects of the ketogenic diet on the human body, we are slowly learning more about the positive effects of ketone bodies on overall brain health and the potential therapeutic benefits against various neurogenic conditions.

EPILEPSY

Epilepsy is a chronic brain disease involving recurrent epileptic seizures. The pathogenesis of epilepsy is based on the predisposition of brain tissue to generate electrical impulses that lead to neuronal hyperstimulation and induce hyperactivity of different brain areas. An epileptic seizure is not synonymous with epilepsy. Epilepsy affects people of different sexes, ages and races. However, it is one of the most common childhood neurological diseases. The incidence is influenced by genetic, environmental and physiological factors. In one third of cases, drug treatment does not lead to seizure relief. There have been a number of studies that have shown the possible efficacy of the ketogenic diet in drug-resistant epilepsy. The ketogenic diet stabilises the body's glucose and insulin levels. Ketone bodies cause regeneration of nerve cells, mitigate inflammatory reactions and neutralise oxidative stress. Following a ketogenic diet, ATP production increases, which stimulates potassium channels and thus reduces neuronal activity. By decreasing aspartate, the synthesis of GABA, an inhibitory neurotransmitter, is increased. Medium chain triglycerides (MCTs) also have a positive effect. They increase the plasma concentration of decanoic acid, which in turn inhibits the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor and thus has an even better anticonvulsant effect than ketones.

A 2020 publication described how adding MCTs to the diet (twice daily for three months) reduced the frequency of epileptic seizures in 42% of adult patients. The study showed that a diet with MCTs has a beneficial effect in people who do not classify for a classical ketogenic diet [5]. Some experts recommend the implementation of a ketogenic diet in people with epilepsy when two anti-epileptic drugs have failed. In some diseases such as GLUT-1 deficiency syndromes or pyruvate dehydrogenase deficiency, experts recommend including the diet earlier.

A study involving 160 children with drug-resistant epilepsy was conducted in 2022. They were put on a ketogenic diet and the effects were monitored for 24 months. In this study, absence of seizures was observed in 13.7 % of the children after 3 months, in 12.5 % of the children after 6 months, in 14.4 % after 12 months and in 10.6 % after 24 months. A 50% reduction in seizure intensity was also observed in 41.9% of children after 3 months, in 37.5% after 6 months, in 28.7% after 12 months and in 16.2% after 24 months. A reduction in the number of seizures along with a complete absence of seizures was shown in up to 48.31% of children [6].

ALZHEIMER'S DISEASE

Alzheimer's disease is the most common cause of dementia in older people. It is a heterogeneous and multifactorial disease characterised by cognitive impairment, confusion, progressive memory loss and personality changes. Alzheimer's disease develops over many years, often without showing specific symptoms in its early stages. The aetiopathogenesis of Alzheimer's disease is not fully understood. It is suggested that both environmental and genetic factors influence its development. The aetiopathogenesis of this disease has been linked to hypometabolism, mitochondrial dysfunction, inflammation, oxidative stress, blood-brain barrier disruption and cerebral atherosclerosis. In addition, genome-wide studies (GWAS) have shown that up to about 20 genetic sites may be associated with the risk of developing the disease [7]. Brain deposits

laden with amyloid β (Aβ) and intrinsic neurofibrillary tangles consisting of tau protein are important hallmarks of Alzheimer's disease. Studies report that Aβ directly affects the impairment of the glycolytic pathway and the tricarboxylic acid cycle. It can be said that patients with Alzheimer's disease show features of insulin resistance in the brain. Three pathologies have been suspected: reduced insulin transport to the brain, reduced insulin levels in the brain and faulty insulin receptors in the brain [8]. Dr Weinstein et al. observed a reduction in the volume of the grey matter in young people with hyperglycaemia. At the same time, Dr Kerti et al. observed a reduction in hippocampal volume. Thus, it can be concluded that hyperglycaemia leads to changes in the brain, causing memory impairment [4]. A randomised study of 26 patients diagnosed with Alzhaimer's Disease who were put on a ketogenic diet for 12 months showed an increase of an average of 5 points on the ACE III (Addenbrooke's Cognitive Functioning Scale) and an average of 2 points on the ADCS-AD (Everyday Functioning Scale) in tests performed at the end of therapy compared to tests performed before the introduction of the ketogenic diet [9]. While in one study by Mélanie Fortier et al. in which Alzhaimer's patients were given a ketogenic drink for 6 months, it was observed that improved scores on tests of cognitive function were directly and significantly correlated with increased levels of ketones in the blood and with increased uptake of ketones by the brain.

MIGRAINE

The Global Burden of Disease, Injury and Risk Factors Study continues to identify migraine as the leading cause of disability worldwide, particularly in people under 50 years of age. It is worth noting that disorders often co-occurring with migraine, such as neck pain, depression and anxiety, are also among the top ten causes of disability worldwide. This condition affects about 12% of the world's population, and its chronic form occurs in 1-2% of people worldwide. Of those struggling with episodic migraine, 2.5% of patients develop the chronic form [10]. Migraine manifests as frequent paroxysmal, very severe headaches, which may be accompanied by vegetative symptoms such as headache that worsens with movement, nausea, vomiting and hypersensitivity to environmental stimuli. It is a condition that significantly affects patients' quality of life and daily functioning. People with migraine also have a higher risk of developing comorbidities such as depression, anxiety, bipolar affective disorder, fibromyalgia, sleep disorders or cardiovascular disease. Although the exact causes of migraine are not yet fully understood, there is speculation that mitochondrial dysfunction and associated difficulties in ATP production may be one potential mechanism for this ailment. Several studies have confirmed the presence of a deficiency in energy production with an increase in energy consumption in migraine patients. It was discovered that an increase in energy demand beyond a certain threshold creates metabolic and biochemical conditions for the onset of a migraine attack, and that the hypoglycaemic state prolongs the occurrence of depression of electrical impulse propagation in the cerebral cortex [11]. In 2022, Carlo Lovati et al. conducted a study on 21 patients diagnosed with drug-resistant migraine. The subjects were divided into two groups: the first followed the guidelines of a ketogenic diet, the second a low-carbohydrate diet. Patients treated with the ketogenic diet showed a significant reduction in migraine attack frequency, headache intensity and medication intake. No significant benefit was observed in the low-carbohydrate diet group. In the same year, an identical study was conducted on 31 patients diagnosed with drug-resistant migraine, who were also changed to a ketogenic and low-carbohydrate diet. The results were comparable to those of the first study [12].

PARKINSON'S DISEASE

Parkinson's disease is a neurodegenerative disease whose likelihood of occurrence increases with age. It is predisposed by genetic factors, toxins, environmental factors and certain medications. The symptoms of Parkinson's disease include: muscle rigidity, resting tremor and motor retardation. The pathogenesis of Parkinson's disease is thought to be neuronal atrophy in the black matter, responsible for dopaminergic transmission in the striatum and basal nuclei. An additional role in the pathogenesis of the above disease is played by Lewy bodies – abnormal protein aggregates made up of the wrong form of alpha-synuclein.

The primary drug in this disease is levodopa. There have been studies showing that a ketogenic diet increases the bioavailability of levodopa [13]. At the same time, it has been observed that the ketogenic diet affects the activation of KATP channels located on GABAergic neurons, contributing to an increase in alpha synuclein synthesis [14].

The gut microbiota is also altered in Parkinson's disease. The ketogenic diet modifies the gut microbiota by increasing the number of Prevotella family bacteria and decreasing the number of Enterobacteriaceae family bacteria, contributing to an increased anti-inflammatory effect by reducing the occurrence of oxygenic stress in the gastrointestinal tract. There are also stud-

ies showing that the ketogenic diet alone reduces the mortality of dopaminergic neurons. In some studies, improvements in mood and balance, improved motor function and a reduction in tremor were observed in just 28 days after the ketogenic diet [15]. In others, improvements in speech and short-term memory were observed in study participants [16].

DEPRESSION

Depression is the fourth most serious illness globally, according to data from the World Health Organization (WHO), with approximately one-third of patients exhibiting resistance to pharmacological treatment. This condition affects individuals of all genders, races, and age groups. Stressful life events such as the death of a loved one, loss of employment, or the end of a relationship can contribute to its onset.

The pathogenesis of depression is primarily associated with disturbances in serotonin secretion, which in turn results from abnormalities in the metabolism of tryptophan, the amino acid precursor of serotonin. Deficiencies in other neurotransmitters are also implicated in the development of depressive disorders. These include gamma-aminobutyric acid (GABA), substance P, and brain-derived neurotrophic factor (BDNF).

The ketogenic diet includes a variety of foods rich in tryptophan. It has been observed that adherence to this dietary regimen increases the production of GABA, a neurotransmitter with calming effects that also enhances the efficacy of medications such as benzodiazepines [17]. However, studies have also shown that the ketogenic diet may reduce the abundance of gut bacteria such as *Bifidobacterium* and *Lactobacillus*, which are capable of synthesizing neurotransmitters; their depletion may contribute to the development of depressive symptoms [18].

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disorder and one of the leading causes of disability among young adults. The incidence of this disease is steadily increasing, with a growing number of cases reported each year. In MS, the myelin sheath surrounding neurons becomes damaged, leading to disturbances in motor and sensory functions.

The ketogenic diet has shown promise in supporting the regeneration of myelin. The ketone body β-hydroxybutyrate crosses the blood-brain barrier and enhances the synthesis of brain-derived neurotrophic factor (BDNF), a key agent in promoting myelin growth. It has also been demonstrated that serum glucose levels are inversely correlated with BDNF concentrations[19]. The most significant effects were observed with the Mediterranean variant of the ketogenic diet, which was associated with increased activation of the CREB transcription factor, thereby boosting BDNF production [20] .

Another observed effect of the ketogenic diet was its impact on serum neurofilament light chain (sNfL), a biomarker used in MS diagnosis. After six months of adherence to the ketogenic diet, a decrease in sNfL levels was noted, indicating a neuroprotective effect [21]. Furthermore, reductions in cyclooxygenase enzymes (COX-1 and COX-2) and proinflammatory cytokines were observed following dietary intervention [22]. Improvements were recorded in both physical and mental health, including enhanced well-being and alleviation of depressive symptoms.

LIMITATIONS AND POTENTIAL ADVERSE EFFECTS OF THE KETOGENIC DIET

A primary limitation of this study is the limited number of available scientific investigations addressing the effects of the ketogenic diet in the context of MS. The most extensively studied neurological condition in relation to the ketogenic diet remains epilepsy. This disparity arises from the relatively recent expansion of research into neurological disorders beyond epilepsy. Nevertheless, despite the small body of research, the effects observed to date are compelling enough to justify further exploration in this domain.

The ketogenic diet also presents practical challenges. Clinical trials have reported difficulties in patient adherence, which can compromise its long-term effectiveness. In a multi-year study on the impact of the ketogenic diet on seizure severity, the most common reasons for early discontinuation were lack of motivation, poor compliance, and worsening of seizure symptoms [23].

Although rare, the ketogenic diet can also result in side effects such as nausea, vomiting, and hypoglycemia. These adverse effects are well-documented in a 2020 meta-analysis involving 932 participants (711 children and 221 adults) with diagnosed epilepsy [24]. Gastrointestinal symptoms—including diarrhea, nausea, and vomiting—were the most frequently reported. Among children, additional side effects included weight loss, recurrent infections, and increased drowsiness, while adults most commonly reported headaches, abdominal pain, and an elevated risk of kidney stone formation. In women, irregular menstruation was also noted.

Another 2020 study involving 158 children—126 of whom had epilepsy with an average age of 4.6 years—found that the most frequent adverse effect was vomiting, reported in 80% of cases. Hypoglycemia below 40 mg/dL occurred in 44 patients, while six experienced

excessive ketosis with urinary ketone levels reaching 160 mg/dL [25].

In patients with Parkinson's disease, some reported increased irritability, hunger, and thirst. However, it is important to emphasize that the so-called "keto flu" is a temporary and self-limiting condition that does not pose a serious health threat [26].

CONCLUSIONS

The presented work provides an integrated compilation of currently available studies analyzing the impact of the ketogenic diet and underscores the importance of continuing research to achieve a fuller understanding of the mechanisms of action of this diet and its potential therapeutic benefits.

REFERENCES

1. Wheless JW, History of the ketogenic diet. Epilepsia. 2008:49(8):3-5. doi: 10.1111/j.1528-1167.2008.01821.x. DOI
2. Puchalska P, Crawford PA, Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics, Cell Metab. 2017;25(2):262–284. doi: 10.1016/j.cmet.2016.12.022. DOI
3. Pondel N, Liśkiewicz D, Liśkiewicz A. Dieta ketogeniczna – mechanizm działania i perspektywy zastosowania w terapii: dane z badań klinicznych. [Ketogenic diet – mechanism of action and perspectives of application in therapy: data from clinical trials]. Postepy Biochem. 2020;66(3):270-286, doi: 10.18388/pb.2020_342. (Polish) DOI
4. Pietrzak D, Kasperek K, Rękawek C et al. The Therapeutic Role of Ketogenic Diet in Neurological Disorders. Nutrients. 2022;14(9):1952, doi:10.3390/nu14091952. DOI
5. Yeou-mei CL, Huei-Shyong W. Medium-chain triglyceride ketogenic diet, an effective treatment for drug-resistant epilepsy and a comparison with other ketogenic diets. Biomed J. 2013;36(1):9-15. doi: 10.4103/2319-4170.107154. DOI
6. Perna S, Ferraris C, Guglielmetti M et al. Effects of Classic Ketogenic Diet in Children with Refractory Epilepsy: A Retrospective Cohort Study in Kingdom of Bahrain. Nutrients. 2022;14(9):1744. doi: 10.3390/nu14091744. DOI
7. Rusek M, Pluta R, Ułamek-Kozioł M et al. Ketogenic Diet in Alzheimer's Disease. Int J Mol Sci. 2019;20(16):3892. doi: 10.3390/ijms20163892. DOI
8. Takeishi J, Tatewaki Y, Nakase T et al. Alzheimer's Disease and Type 2 Diabetes Mellitus: The Use of MCT Oil and a Ketogenic Diet Int. J. Mol. Sci. 2021;22(22):12310. doi:10.3390/ijms222212310. DOI
9. Phillips MCL, Deprez LM, Mortimer GMN et al. Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease. Alzheimers Res Ther. 2021;13(1):51. doi: 10.1186/s13195-021-00783-x. DOI
10. Dyńka D, Kowalcze K, Paziewska A. The Role of Ketogenic Diet in the Treatment of Neurological Diseases, Nutrients. 2022;14(23):5003. doi: 10.3390/nu14235003. DOI
11. Cevoli S, Favoni V, Cortelli P. Energy Metabolism Impairment in Migraine, Curr Med Chem. 2019;26(34):6253-6260. doi: 10.2174/0929867326566180622154411. DOI
12. Lovati C, D'Alessandro CM, Della Ventura S et al. Ketogenic diet in refractory migraine: Possible efficacy and role of ketone bodies—A pilot experience. Neurol Sci. 2022;43(11):6479-6485. doi: 10.1007/s10072-022-06311-5. DOI
13. VanItallie TB, Nonas C, di Rocco A et al. Treatment of Parkinson Disease with Diet-Induced Hyperketonemia: A Feasibility Study. Neurology. 2005;64(4):728-30. doi: 10.1212/01.WNL.0000152046.11390.45. DOI
14. Emmanouilidou E, Minakaki G, Keramioti MV et al. GABA Transmission via ATP-Dependent K+ Channels Regulates α-Synuclein Secretion in Mouse Striatum. Brain. 2016;139:871-90. doi: 10.1093/brain/awv403. DOI
15. Krikorian R, Shidler MD, Summer SS et al. Nutritional ketosis for mild cognitive impairment in Parkinson's disease: A controlled pilot trial. Clin Park Relat Disord. 2019:1:41-47. doi: 10.1016/j.prdoa.2019.07.006. DOI
16. Vanitallie TB, Nonas C, Di Rocco A et al. Treatment of Parkinson disease with diet-induced hyperketonemia: a feasibility study, Neurology. 2005;64(4):728-30. doi: 10.1212/01.WNL.0000152046.11390.45. DOI
17. Melø, TM, Nehlig A, Sonnewald U. Neuronal–Glial Interactions in Rats Fed a Ketogenic Diet. Neurochem Int. 2006;48(6-7):498-507. doi: 10.1016/j.neuint.2005.12.037. DOI
18. Kuwahara A, Matsuda K, Kuwahara Y et al. Microbiota-Gut-Brain Axis: Enteroendocrine Cells and the Enteric Nervous System Form an Interface between the Microbiota and the Central Nervous System. Biomed Res. 2020;41(5):199-216. doi: 10.2220/biomedres.41.199. DOI
19. Lee D-H, Geyer E, Flach A-C et al. Central nervous system rather than immune cell-derived BDNF mediates axonal protective effects early in autoimmune demyelination. Acta Neuropathol. 2012;123(2):247-58. doi:10.1007/s00401-011-0890-3. DOI
20. Vauzour D. Polyphenols and brain health. OCL. 2017;24(2). doi: 10.1051/ocl/2017008. DOI
21. Bock M, Steffen F, Zipp F et al. Impact of Dietary Intervention on Serum Neurofilament Light Chain in Multiple Sclerosis. Neurol Neuroimmunol Neuroinflamm. 2021;9(1):e1102. doi: 10.1212/NXI.0000000000001102. DOI
22. Bock M, Karber M, Kuhn H. Ketogenic diets attenuate cyclooxygenase and lipoxygenase gene expression in multiple sclerosis. EBioMedicine. 2018:36:293-303. doi: 10.1016/j.ebiom.2018.08.057. DOI

23. Kverneland M, Selmer KK, Nakken KO et al. Prospective Study of the Modified Atkins Diet for Adults with Idiopathic Generalized Epilepsy. Epilepsy Behav. 2015:53:197-201. doi: 10.1016/j.yebeh.2015.10.021. DOI
24. Martin-McGill KJ, Bresnahan R, Levy RG al. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev. 2020;6(6):CD001903. doi: 10.1002/14651858.CD001903.pub5. DOI
25. Lin A, Turner Z, Doerrer SC et al. Complications During Ketogenic Diet Initiation: Prevalence, Treatment, and Influence on Seizure Outcomes. Pediatr Neurol. 2017:68:35-39. doi: 10.1016/j.pediatrneurol.2017.01.007. DOI
26. Bostock ECS, Kirkby KC, Taylor BV et al. Consumer Reports of "Keto Flu" Associated With the Ketogenic Diet. Front Nutr. 2020:7:20. doi: 10.3389/fnut.2020.00020. DOI

CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Piotr Kucharczyk
Medical University of Warsaw
61 Żwirki i Wigury St., 02-091 Warsaw, Poland
e-mail: piotr.kucharczyk97@gmail.com

ORCID AND CONTRIBUTIONSHIP

Piotr Kucharczyk: 0009-0005-7382-9690 D
Kinga Szczepanik: 0009-0007-5395-7366 A D
Karolina Parzęcka: 0009-0007-2284-1221 B D
Anna Żerańska: 0009-0003-1208-2007 B F
Mateusz Michalak: 0009-0002-5495-4670 E F
Bartłomiej Kusy: 0009-0000-8355-2262 B F
Olaf Domaradzki: 0009-0000-0533-9386 F
Wojciech Bieńkowski: 0009-0005-1776-8862 A B F
Julia Charkot: 0009-0000-1224-3251 E F

A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 15.05.2025
ACCEPTED: 20.07.2025