REVIEW ARTICLE

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Effects of ketogenic diet on epilepsy in children

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Abstract

Introduction and Objective. The Ketogenic Diet (KD) is a diet consisting of the restriction of protein, carbohydrates, and fluids. KD is used in the treatment of epilepsy and is currently the foundation for a therapeutic approach for drug-resistant epilepsy. The aim of the study was to review the current literature, and provide information about the application of the Ketogenic Diet in children with treatment-resistant epilepsy.

Review Methods. Literature in English and Polish was reviewed via PubMed, Google Scholar and The Wiley Library. 250 publications were taken into consideration from which 50 were selected: meta-analysis publications, review articles, randomised controlled trials, and research articles, with emphasis on the most recent information on the topic. About 88% of the publications selected were published in 2017 or later.

Brief description of the state of knowledge. Taking into consideration randomised controlled trials of 472 children with drug-resistant epilepsy, the results indicate a statistically significant reduction in seizure frequency (SFR ≥ 50%) in the KD-treated group, compared to the control group. The greatest improvement was observed in patients following a KD with a ketogenic ratio of 2.5/3:1 and the optimal time to initiate KD being before the age of two years. The highest chance of success was noted in the infant population in whom a complete elimination of epileptic seizures is possible.

Summary. Randomised controlled trials indicate that the Ketogenic Diet has a positive effect on reducing the occurrence of seizures in paediatric patients with drug-resistant epilepsy.

Key words

drug-resistant epilepsy, ketone bodies, Ketogenic Diet, paediatric epilepsy, seizure control, Modified Atkins Diet.

INTRODUCTION AND OBJECTIVE

Epilepsy is the one of the many complex and persistent chronic neurological disorders, pathologically characterised by sudden, abnormal electrical discharges that can lead to a transient brain dysfunction [1]. The prevalence of epilepsy is estimated to be 0.5–1.0%, making it the most common chronic neurological disorder of the childhood period [2]. The illness is marked by various types of seizures, defined as transient subjective and objective symptoms, resulting from abnormal, excessive, or synchronous neuronal activity in the brain [3]. Among the types of epilepsy, one can distinguish those that are drug-resistant, requiring a unique therapeutic approach for seizure control – the Ketogenic Diet (KD).

The Ketogenic Diet has been effectively employed since the 1920s on a broad scale for treating children who continue to experience seizures, despite pharmacological treatment with anti-epileptic drugs (AEDs) [4]. KD aims to mimic the fasting state in the body without the negative effects of starvation. Such a condition can be achieved by reducing the production of energy from glucose in exchange for energy obtained as a result of increased oxidation of fatty acids and ketone bodies formed in this process [5].

The positive effects of implementing KD in patients with drug-resistant epilepsy have been demonstrated through randomised trials and meta-analyses, in which approximately 50% of children with drug-resistant epilepsy experienced a 50% reduction in seizures through the use of the diet [4, 6]. The aim of the study is to review the current literature and provide information on the impact of KD on epilepsy in children, and to present side-effects resulting from its use, as well as to show the results of studies on the effectiveness of KD therapy in children with drug-resistant epilepsy.

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REVIEW METHODS

The review was based on scientific publications acquired via a comprehensive search strategy using the key words: 'Ketogenic Diet', 'paediatric epilepsy', 'seizure control', 'Modified Atkins Diet', 'drug-resistant epilepsy', and 'ketone bodies'. The search was performed using the databases PubMed, Google Scholar and The Wiley Library. The publications selected included meta-analyses, reviews, randomised controlled trials, and research articles. A total of 250 publications were considered, and those that were not available in full, were not in Polish or English, were rejected. Finally, 50 publications in Polish or English were selected, with an emphasis on the most recent information on the topic. Of these, about 88% were published in 2017 or later, while only 12% had been published before 2017.

Fundamentals of the Ketogenic Diet and its variants. The basis of the Ketogenic Diet (KD) is limitation of the supply

of carbohydrates, protein and fluids, and shifting the main energy source to fats [6]. The KD places the patient into a state of ketosis, which is defined as an increase in the concentration of ketone bodies, such as hydroxybutyric acid, acetoacetic acid and acetone in the blood plasma, without changing in the body's insulin production and with a stable physiological glycaemia. KD is considered a risky diet because, if improperly monitored and controlled, it can lead to ketoacidosis [7]. The calculation of the classic KD is assumed as the ratio of the intake of fats to the protein and carbohydrates intake. The most common KDs are those with ratios of 4:1 (for every 4g of fat consumed, 1g of protein with added carbohydrates) or 3:1 [8]. This ratio of food intake allows for the shift of the main metabolic energy production pathway to the production of ketone bodies from fats. A typical calorie intake in KD is limited to 80–90% of calories recommended for age, fluid intake is limited to 90% of the recommended intake. Moreover, when using KD, it is crucial to take into consideration supplementing minerals and vitamins as they are in decline [6–11].

The modified Atkins Diet is a relatively new and improved form of the classic Ketogenic Diet, the main difference being the ratio of fats to protein with carbohydrates in the Atkins, as well as the initiation of the diet [11]. Throughout the diet, the ratio of fats to carbohydrates is 1:1. Unlike the classic form of KD, the modified Atkins Diet does not impose any restrictions on the patient's fluid, protein nor calorie intake, allowing the patient to freely plan meals and have greater nutritional options. Additionally, patients using this diet do not require such intensive vitamin supplementation [9, 10–12].

Low Glycaemic-Index Therapy (LGIT). A transformed form of the classic ketogenic diet based on the phenomenon that patients during KD, have a reported constant physiological glycaemic value [12]. This form of KD is based on a ratio of 0.6:1 (fats: carbohydrates). The carbohydrates served must be classified as carbohydrates with a low glycaemic index (<50), such as green vegetables, tomatoes, raw carrots, soy pasta or whole grain rye bread. Initiating the diet does not require hospitalisation nor extensive changes in the amount of carbohydrates or fats consumed. The main criteria examined in the described diet is glycaemia because the diet causes a small increase in ketones and is considered to be better tolerated by patients than the classic form of KD, with similar effectiveness in illness control [9, 12].

Each case of KD use is tailored to the patient's needs. Before implementing the diet, a detailed interview is conducted with the patient or the patient's caregiver. The interview includes all co-existing diseases, all medications taken, treatment history, all difficulties encountered in the treatment of epilepsy, the patient's psycho-social condition, and the expectations of the patient regarding the treatment. Additionally, it is crucial to perform laboratory tests, such as a complete blood count, electrolyte panel, including total protein count, a liver enzyme panel (ALT, AST, albumin), renal marker tests (creatinine, urea nitrogen) and urine analysis [7, 9, 12].

Biochemistry aspects of the Ketogenic Diet during the preliminary phase. During the initiation of a Ketogenic Diet, blood glucose levels decrease and then stabilise, inhibiting insulin release and inducing the body into a state of catabolism. In such instances, free fatty acids serve as the primary source of energy [13]. During the oxidation of fatty acids in the mitochondria, acetyl-CoA is produced, further serving as the precursor for the synthesis of ketone bodies (mainly acetone and beta-hydroxybutyrate) in the liver. The resulting compounds are then transported into the bloodstream [13]. The brain can utilise ketone bodies produced in the oxidation process of free fatty acids in situations where the glucose concentration in the body is insufficient [14]. Ketone bodies delivered to the brain via the bloodstream are transformed into acetyl-CoA, which is incorporated into the Krebs cycle within the mitochondria, resulting in the production of ATP [15]. Although the brain exhibits reduced dependence on glucose when the concentration of ketone bodies in the body is between 2–4 mM, they can only satisfy up to 60% of the brain's energy requirements [16].

Mechanism of action of the Ketogenic Diet in the treatment of epilepsy. The mechanism of action of the ketogenic diet in epilepsy is not fully understood; however, numerous sources suggest that the ketogenic diet and polyunsaturated fatty acids play a crucial role in generating anti-epileptic effects, leading to a reduction in seizure frequency [14]. It is likely that the therapeutic success involves various factors, such as changes in neuronal metabolism, alterations in the quantity and type of neurotransmitters and ion channels in the neuronal cell membrane, hyperpolarization of the neuronal cell membrane, and a reduction in oxidative stress [17]. Metabolic changes in the blood and cerebrospinal fluid (decrease in glucose levels and an increase in ketone body levels), modulation of mitochondrial metabolism, and energy reserve, have also been observed. These and many other factors are likely contributors to synaptic stabilisation and a decrease in neuronal excitability [14] (Tab. 1).

Ketone Bodies (acetone, beta-hydroxybutyrate) are by-products of the oxidation of fatty acids occurring in the mitochondrial matrix of hepatocytes. An increase in their concentration in the blood is the most characteristic biomarker of a properly applied Ketogenic Diet [21]. The anti-epileptic action of ketone bodies has been verified in some preclinical studies conducted on rodents, but their impact on seizure control turned proved to be minimal [18]. However, beta-hydroxybutyrate interacted with several novel molecular targets, such as histone deacetylases, hydroxycarboxylic acid receptors on immune cells, NLRP3 inflammasomes, as documented in research [21].

Modulation of mitochondrial metabolism. Ketone bodies provide a greater amount of energy than glucose. Scientists report that they may stimulate the regulation of genes involved in metabolic processes, thereby enhancing the function of mitochondria in neurons [14]. Undisturbed ATP production ensures a constant energy supply for nerve cells, contributing to the proper functioning of ion channels and neurotransmitters, maintaining neuronal balance [21].

Neuronal metabolism and synaptic functionality. Under normal conditions, glucose serves as the substrate for nerve cells. Glucose molecules need to traverse the blood-brain barrier, facilitated by glucose transporters present in the endothelium of brain capillaries. This metabolic pathway generates rapidly available energy necessary for triggering epileptic seizures. In patients adhering to a Ketogenic

Table 1. Possible Antiepileptic Mechanisms of the Ketogenic Diet [17–20]

Key changes	Possible antiepileptic mechanism
Increase in ketone body production [17]	• Increased production of inhibitory neurotransmitters and reduction in neuronal excitability • Changes in energy metabolism for improved neuronal homeostasis • Neuronal hyperpolarization through activation of ATP-dependent K+ channels and multi-domain potassium channels • Slow production of energy from ketone bodies with antiepileptic effects
Increased concentration of polyunsaturated fatty acids [17]	• Activation of peroxisome proliferator-activated receptors (PPARs) • Neuronal hyperpolarization through modulation of ion channels • Increase in uncoupling proteins and reduction in reactive oxygen species production
Protection against apoptosis and cell death, inhibition of proapoptotic factors [17]	• Increase in calbindin concentration • Inhibition of pore formation in the mitochondrial membrane • Inhibition of pro-apoptotic factors (e.g., caspase-3)
Modification of gut microbiota [19]	• Possible increase in seizure threshold (via increased bacterial numbers, such as Akkermansia muciniphila, Parabacteroides)
Alterations in the production of inflammatory mediators and anti-inflammatory factors [18]	• Reduced production of interleukin 1β and other cytokines (mouse model studies)
Increased production of inhibitory neurotransmitters [20]	• GABA, agmatine, monoamines, galanin, neuropeptide Y, and adenosine A1 induce presynaptic inhibition and hyperpolarization by activating postsynaptic potassium channels • Increase in GABA concentration in the cerebrospinal fluid • Decrease in asparagine levels (an inhibitor of glutaminase, which catalyses the precursor of GABA – alpha-ketoglutarate)

Diet, blood glucose levels are low and constant, and the brain utilises ketone bodies provided by the diet for energy production. This metabolic approach slows down the availability of energy, consequently reducing the frequency of seizures. This has been confirmed in experimental models, where the administration of 2-deoxy-D-glucose increased the seizure threshold, and the administration of glucose reversed this effect [22].

Impact on neurotransmission, neurotransmitters, ion channels and their functions. Under the conditions of a Ketogenic Diet, reduced utilisation of glucose by the brain and decreased ATP production through glycolysis may lead to the opening of ATP-dependent K+ channels, resulting in hyperpolarization of the neuronal membrane and a reduction in the electrical excitability of the brain [17]. Two-pore domain potassium channels (K2P, leak potassium channels) allow a spontaneous efflux of potassium ions through the cell membrane, and may directly influence the duration and frequency of neuronal discharges. Studies report that they are regulated by physical, chemical, natural factors, as well as by ketone bodies and certain fatty acids, potentially making them one of the mechanisms of action of the Ketogenic Diet [17]. The diet increases the expression of glutamic acid decarboxylase and may also influence the metabolism and levels of glutamate, agmatine, monoamines (norepinephrine, serotonin, dopamine) in the brain [23]. Although the exact mechanisms have not yet fully understood, the impact of the ketogenic diet on modulating neurotransmitter activity is highly probable [17].

The kynurenine pathway generates a series of metabolites, collectively known as kynurenines, which participate in inflammatory states, immune responses, and central nervous system disorders, such as epilepsy, depression, and neurodegenerative diseases [24]. Over-production of ketone bodies during the use of a Ketogenic Diet, reduces the inhibitory influence of glutamate on the formation of kynurenic acid, an endogenous neuroprotective agent [24]. It has also been demonstrated that the implementation of a Ketogenic Diet significantly increases the concentration of kynurenic acid in the hippocampus and striatum in young and adult rats [21]. Blood studies measured the levels of tryptophan, kynurenine, kynurenic acid and 3-OH-kynurenine at 3, 6 and 12 months on the diet, and compared them to pre-KD levels. Among patients adhering to a KD and reporting a reduction in the frequency of epileptic seizures, significant changes were observed, such as higher levels of kynurenic acid and lower levels of kynurenine [24].

Intestinal microbiome. There is still limited research assessing the impact of a KD on the human gut microbiota. However, observations in mice have indicated an enrichment of the microbiome in such species as Akkermansia and Parabacteroides. These changes were seen to restore protection against seizures in mice. Moreover, transplanting the microbiome had a similar impact on the epilepsy models in mice fed a control diet (which included larger amounts of amino acids and smaller amounts of fatty acids than the KD) [19]. Results from studies reveal that the KD alters the gut microbiota, promoting select microbial interactions that reduce bacterial gamma-glutamylation activity, decrease peripheral GG-amino acids and elevate hippocampal GABA/glutamate ratios. All these changes have potential anti-epileptic effects on the hippocampus, a brain region important for the propagation of seizure activity. Differences in the gut microbiota between healthy individuals and those experiencing epileptic seizures are noticeable, and dietary modifications may contribute to better disease control [19].

Anti-inflammatory and anti-oxidant effects. The Ketogenic Diet increases the availability of glutathione within cells, thereby protecting mitochondrial DNA from oxidative stress. This mechanism prevents damage to nerve cells during epileptic discharges [25]. Additionally, the KD positively regulates the levels of anti-oxidant genes, functions of coupling proteins and can reduce the production of reactive oxygen species [13]. The ultimate result of the anti-inflammatory and anti-oxidant actions achieved through the KD is an improvement in the resilience of nerve cells to excessively high levels of reactive oxygen species generated during seizures [26].

Localised changes in pH. Ketone metabolism leads to the production of metabolites that can lower the local pH of the environment, which may be another potential way in which KD affects brain function. Unfortunately, there is no definitive evidence that the KD lowers the pH level in the brain. Nevertheless, many receptors involved in generating abnormal energy discharges (e.g. ASIC1a, NMDA, and GABA receptor isoforms) are regulated by pH, which could influence the effectiveness of the Ketogenic Diet [21].

The role of glucose. Currently, the most promising influence is attributed to the glycolysis inhibitor, 2-deoxyglucose. More research confirming the hypothesis about the influence of glucose on the occurrence of epileptic seizures is needed, but new research indicates that 2-deoxy-D-glucose may have anti-convulsant effects through interaction with netrin-G1 and activation of K-ATP channel [22].

Success of the Ketogenic Diet in child-onset epilepsy. Use of the diet in treating epilepsy in children to assess its effectiveness and safety has been the subject of many clinical studies over the years. In the analysis of 5 randomised clinical trials involving a total of 472 children with drug-resistant epilepsy, a reduction in seizure frequency (SFR > 50%) was observed in 35–56.1% of participants in the treatment groups, compared to 6–18.2% in the control groups. In the treatment group, a classical KD and/or modified Atkins diet were implemented [27]. One of the newest meta-analysis conducted by Evangelia Desli et al. showed a statistically significant reduction in seizure frequency: >50% in the KD group compared to the control group in 6 out of the 14 considered studies [28].

The effectiveness of KD was also observed in infants. Initiating KD therapy below the age of 2 years may be optimal due to the metabolic advantage of infants. Children under 1.5 years have a higher chance of becoming seizure-free than those over 1.5 years. An exceptionally high likelihood of seizure remission was observed in the infant group below 9 months of age. Another study with patients who started KD before the age of 1 year have demonstrated that the absence of seizures within the first 3 months of treatment may be a grand predictive factor for long-term seizure freedom [29]. A similar study consisting of patients under 3 years of age, suffering from drug-resistant epilepsy of various etiologies showed that patients with a genetic etiology responded exceptionally well to KD therapy [30]. Moreover, most studies indicate a high effectiveness of KD in treating specific epilepsy syndromes, such as West Syndrome, epilepsy with atonic-myoclonic seizures, and Dravet Syndrome [10, 31–32].

The efficacy of the therapy also depends on the type of KD and the ratio of fats to carbohydrates in the food intake. In 2 clinical studies, the Classic Ketogenic Diet (CKD) was slightly (but not statistically significant) more effective than a Modified Atkins Diet (MAD) after 6 months of treatment. Regarding the fats to carbohydrates ratio in KD, 2 randomised studies showed greater effectiveness with a ratio of 2.5:1 or 3:1, compared to 4:1. According to the latest research in patients with a lipids to carbohydrates ratio in KD therapy of 2.5:1 or 3:1, a higher percentage experienced a >50% reduction in seizures, and tolerance to therapy was better than in the 4:1 group [28].

Negative side-effects. Ketogenic diet plays a significant role in the therapeutic process of epileptic seizures. Despite its satisfactory therapeutic effect on many patients who use it, numerous side-effects can be observed. According to one of the latest reviews, they primarily affect systems such as the gastrointestinal, cardiovascular, urinary, haematologic and skeletal systems, as well as the skin and liver. Common complications in the initial phase of the diet include vomiting, hypoglycaemia, and metabolic acidosis, which often lead to the patient refusing to follow the recommended treatment [33].

Gastro-intestinal complications. In a retrospective study by Abigail Lin etal. in a group of 158 children, the most frequently reported negative side-effects related to KD therapy were gastrointestinal complications, including nausea, emesis, and constipation [34]. These complications are common and mild, but there are a few reported cases of severe and rare states caused by KD therapy, such as pancreatitis, likely resulting from increased lipid levels in the serum [35].

Cardiovascular complications. Such complications induced by KD therapy are rare, with the most serious being prolonged QT intervals and cardiomyopathy. Cardiomyopathy associated with KD results from selenium deficiency, therefore monitoring selenium levels and its supplementation are important aspects for patients who do not consume sufficient amounts of animal products, the primary source of this element [33]. Due to the fact that the KD is rich in fats, there is a concern that it may lead to dyslipidemia and atherosclerosis. A study conducted by Kapetanakis et al. showed a decreased distensibility of the carotid artery and poor lipid profiles at 3 and 12 months after starting KD [33, 36].

Renal complications. Important adverse effects concern kidney stones reported in 3–7% of children on KD therapy. Three studies involving over 200 children revealed that potassium citrate, the supplementation of which prevents metabolic acidosis, led to a reduction in the occurrence of the mentioned complication [33].

Haematologic complications. Haematologic side-effects of KD therapy include neutropenia, increased haemoglobin levels, and decreased platelet activity [33]. A study conducted by Munro et al. found that out of 89 children, 27 developed neutropenia, which was linked to higher levels of urinary ketones and a longer duration of the KD [37]. Interestingly, other studies examining complete blood counts showed normal levels of neutrophils. Additionally, some reports indicated higher levels of haemoglobin, haematocrit, mean corpuscular volume (MCV), and serum vitamin B12, without any apparent clinical issues [7, 38].

Metabolic complications. Numerous studies associate the high-fat content of the KD with metabolic problems, such as hyperlipidaemia. A significant increase in total cholesterol, LDL, VLDL, triglycerides, and total lipoprotein apoB, was observed 6 months after starting KD therapy [33]. However, it may take some time before changes in lipid levels occur and elevated lipid levels may normalise over time [39]. Other metabolic complications of the ketogenic diet therapy include ketoacidosis and a catabolic crisis, which mainly occur in the presence of underlying chronic medical conditions.

Individuals with type 1 diabetes or those subjected to SGLT-2 inhibitors where insulin activity is reduced, are more susceptible to ketoacidosis, which can be exacerbated by a low-carbohydrate diet [40]. Additionally, the use of KDs may trigger an acute catabolic crisis in patients with inborn metabolic defects that impede the transport or oxidation of long-chain fatty acids [12].

Social aspects involving the implementation of the Ketogenic Diet. Introduction of the diet into daily life is both socially and economically challenging. Parents of chronically ill children are at risk of experiencing high levels of stress, particularly when their child has epilepsy [11]. Zanaboni et al. presented a programme called 'Ketoland' in their study which combined the involvement of a multi-disciplinary team of professionals, including a paediatric neurologist, a psychotherapist and a nutritionist. The programme aims to improve parents' and their children's knowledge of the disease and diet through techniques such as storytelling [41].

The most common reason for abandoning the diet was lack of efficacy and dietary intolerance. Other reasons reported by parents were side-effects and loss of KD effect [42]. In addition, patients gave up KD due to acute infections. Children have a less developed immune system and KD itself may contribute to increased susceptibility to infection. This is due to a deficiency of protein, used by the child's body on KD for gluconeogenesis [42].

The successful introduction of KD therapy to a population is influenced by the cultural and dietary preferences of the locality. For example, in places where carbohydrates are the main food component or where vegetarianism is common, it becomes very difficult to maintain this diet and KD is an additional financial burden on the family. Therefore, when KD only slightly improves the patient's condition, the diet is usually abandoned [8].

SUMMARY

Epilepsy is the most common chronic neurological disorder of childhood. This is why it is so important to develop new therapies to reduce seizures.

Analysis of recent publications and meta-analyses of the literature indicates that a significant reduction in seizure frequency in children with drug-resistant epilepsy can be achieved by using KD. The mechanism of action of KD in epilepsy has only been partially revealed and requires further research. The diet is demanding for the child and parents, and may cause side-effects which may lead to abandonment of the diet. However, with recent programmes using a multi-disciplinary approach to the patient, there is hope that this therapy can be better tolerated.

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