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Beyond the seizures: Ketogenic Diets in the battle against drug-resistant epilepsy

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ABSTRACT

Introduction: Epilepsy is a chronic, non-infectious and one of the most common neurological disease. About 70 million people worldwide suffer from it and these are patients of all ages. Despite the existence of many anticonvulsants and multiple lines of treatment, some patients still experience symptoms of the epilepsy. International league against epilepsy says that

one-third of people with epilepsy fail to control it with anti-epileptic drugs (AED) and continue to have seizures.

Purpose: The aim of the study is to analyze the impact of using a ketogenic diet in patients with epilepsy that meets the criteria for drug-resistant epilepsy.

Materials and method: In April 2024, articles found in the Medline (Pubmed) databases were selected by using the following keywords: ketogenic diet in drug-resistant epilepsy, drug-resistant epilepsy, ketogenic diet and selected articles from 2018-2023.

Conclusions: In the ketogenic diet, ketones formed from the oxidation of fatty acids are the source of energy instead of glucose. Ketones increase the amount of inhibitory neurotransmitters and glutathione. It improves neuronal hemostasis and increases cells' resistance during excessive electrical discharges in the brain. These qualities are responsible for the antiepileptic profile of the ketogenic diet. Patients who follow a ketogenic diet experience fewer seizures attacks. We do not know the long-term side effects of the ketogenic diet yet and it is impossible to make a definitive thesis. Scientists are working to prove the validity of ketogenic diet in drug-resistant epilepsy.

KEY WORDS

drug-resistant epilepsy; ketogenic diet; ketogenic diet in drug-resistant epilepsy

INTRODUCTION AND PURPOSE

Epilepsy is a chronic, non-infectious disease of the brain. It is one of the most common neurological diseases. Data shows that between 50 and 70 million people worldwide suffer from it and these are patients of all ages. About 5 million people are diagnosed with epilepsy each year. The cause of the disease is still unknown in about 50% of cases worldwide. 70% of patients are able to live without any seizures (if the disease is properly diagnosed and treated with individually selected therapy). The causes of epilepsy can be various: structural, genetic, infectious, metabolic, immunological and idiopathic.

Epilepsy is characterized by recurrent seizures that are the result of excessive electrical discharges in the brain. The discharges can take place in different parts of the brain. Seizures are episodes of involuntary movements, they can be localized and then affect specific parts of the body, or they can involve the whole body. The severity of attacks also varies, they can be in the form of even very severe convulsions or just a temporary loss of attention. The frequency of seizures varies from patient to patient, according to the WHO, seizures may occur less than once a year, up to several times in one day. Convulsions may be accompanied by loss of consciousness, bowel and bladder dysfunction [1-4].

Two unprovoked seizures or one seizure with a high risk of having more of them can be diagnosed as epilepsy. It should be remembered that not every epileptic seizure is a disease. Their causes may be related to brain damage, familial or idiopathic [5]. Types of epilepsy are divided into two main groups: generalized seizures (located in both hemispheres of the brain, including: absence seizures, myoclonic, atonic, tonic and tonic-clonic seizures) and focal seizures, also called partial seizures (affect one area of the brain, divided into focal without alteration of consciousness, focal with alteration of consciousness and seizures with secondary generalization) [6,7].The aim of this article was to analyze the impact of ketogenic diet (and its modifications) on patients with drug-resistant epilepsy.

Material and methods

In April 2024 scientific articles were reviewed by using Medeline (Pubmed). Articles were searched using keywords: ketogenic diet in drug-resistant epilepsy, drug-resistant epilepsy, ketogenic diet. The available scientific articles and sources were analyzed and 40 were selected for final analysis. The collected knowledge was completed and systematized to achieve the final effect of the review.

DESCRIPTION OF THE STATE OF KNOWLEDGE

Antiepileptic drugs

Many medications are available to prevent or stop seizures. Therapy with anti-epileptic drugs (AEDs) allows control epilepsy with a satisfactory effect in 7 out of 10 people struggling with this disease. The types of therapy are different and drugs are used in combinations selected individually for the patient, age, symptoms and their expected effect [8,9]. AEDs work by changing the levels of chemicals in the brain to stop seizures, but they do not cure epilepsy.

Drugs reduce the likelihood of a pathological discharge by reducing the excitability of the neuron's cell membrane. They can block potential-gated sodium and calcium channels, enhance GABA-ergic transmission, inhibit the release of neurotransmitters from synapses and activate potassium ion channels. A few common drugs used in treatment are sodium valproate, carbamazepine, lamotrigine, levetiracetam, topiramate. AEDs come in the form of tablets, capsules or syrups. Treatment starts with a low dose, which is then gradually increased until the seizures stop. It is important to follow all AEDs instructions and never stop taking them on your own [10-12].

Drug-resistant epilepsy

According to research, about one-third of adults and one-fourth of children fail to control epilepsy with medication (AEDs). The International League Against Epilepsy (ILAE) calls this clinical situation drug-resistant epilepsy where there is no remission of seizures despite the use of two appropriately selected, well-tolerated and administered in appropriate doses of antiepileptic drugs in mono-therapy or in combination.

According to the study, the risk of developing drug-resistant epilepsy is three times higher in patients with symptomatic epilepsy compared to cases with idiopathic epilepsy. In addition to drug-resistant epilepsy (DRE), predisposing factors include neuropsychiatric disorders, mental retardation, neurological disorders, history of febrile seizures, status epilepticus, abnormal electroencephalography (EEG) recording, abnormal neuroimaging findings and an younger age of onset [13,14]. The causes of uncontrollable seizures include, for example: misdiagnosis, non-compliance with recommendations, inappropriate drug doses, incorrectly selected drug, complicating factors.

If all possible causes of the patient's lack of response to treatment have been ruled out, drug-resistant epilepsy can be confirmed. There are several therapeutic options for this type of epilepsy, including: resection surgery (consisting in the surgical removal of the area of the brain generating pathological bioelectric discharges, but not every patient can be qualified for this type of surgery), laser thermotherapy, treatment of a specific genetic cause, immunotherapy, deep brain stimulation, vagus nerve stimulation. A method of treating drug-resistant epilepsy that brings satisfactory results is also the use of a ketogenic diet (KD). It is highly effective for either children or adults. In the treatment of drug-resistant epilepsy, the

Atkins diet (MAD), medium-chain triglycerides diet (MCTD) and the low glycemic index treatment (LGIT) are also applicable [11,15,16].

What is a ketogenic diet?

The Ketogenic Diet (KD), the effectiveness of which has been demonstrated in studies, is based on introducing the body into a state of ketosis. The classic ketogenic diet involves eating mainly high-fat foods. They account for 87-90% of total dietary calories. The amount of protein foods is limited to the minimum requirement as a building material and accounts for about 6% of the diet, and carbohydrates should be kept to a minimum (approx. 4%). In this diet, the ratio of fat to protein and carbohydrate intake should be 4:1. These proportions of ingredients cause a systemic transition from metabolism, where the main substrate for neurons is glucose, to metabolism of fatty acids, in which ketones - acetoacetate and beta-hydroxybutyrate (BHB) become substrates [1,18].

Ketogenic Diet Modifications:

In addition to the classic DC, we distinguish its modifications, also used in the therapy of neurological diseases. The Modified Atkins Diet, or high-protein ketogenic diet, assumes no restriction on the amount of protein and calories consumed. The ratio of fat to carbohydrates and proteins should be around 1-2:1, which makes it much easier to maintain a diet. However, studies have shown a lower effectiveness of MAD compared to classic KD after 3 and 6 months.

The medium-chain triglyceride diet provides faster absorption of triglycerides into the bloodstream and increases the production of ketone bodies. Greater efficiency equals less need for fats and at the same time possible to consume more proteins and carbohydrates. The studies showed that there were no significant differences in the mean seizure rate between the MCTD and classic KD groups after 3, 6 and 12 months of therapy. In addition, the MCTD is more likely to be used by patients, especially children, due to its better taste. In turn, treatment with a low glycemic index diet, although it does not introduce the body into a state of ketosis, has a positive effect on carbohydrate metabolism. It is about replacing products with a high glycemic index (GI), products with a low GI [19-21].

A brief history of the ketogenic diet

The history of the ketogenic diet used in neurological diseases dates back to the 20th century. In 1921, Woodyatt observed that both a high-fat diet and a starvation state put the body into a state of ketosis. In the same year, Russell Wilder at the Mayo Clinic introduced KD as a treatment for epilepsy. It turned out that in more than half of the children suffering from this condition, the state improved. The ketogenic diet was the main therapy used in this group of patients until 1938, when the first dedicated drug was invented – diphenylhydantoin [19].

The biochemical mechanism of the ketogenic diet

Reducing carbohydrates to 50 g/day (and in the initial phase even to 20 g/day) causes biochemical transformations involving the redirection of metabolism to the use of fatty acids as energy substrates. Oxidation of fatty acids (B-oxidation) in the mitochondria of hepatocytes, it results in the generation of a large amount of acetyl-CoA, the significant accumulation of which causes the synthesis of ketone bodies (acetoacetate, BHB). The neurons then use ketone bodies instead of glucose. Once inside the brain cells, the ketones convert to acetyl-CoA, which enters the Krebs cycle in those cells. The result of these reactions is the formation of adenosine 5′-triphosphate (ATP) in neurons [22]. In addition, it has been proven that greater amount of ATP is synthesized from ketones than from glucose, because they increase the number of mitochondria in neurons and glial cells. Thus, despite caloric restrictions, the right amount of energy is supplied to the nerve cells. The resulting surplus of ATP also has a beneficial effect on the amount of neurotransmitters, transporters and the functioning of ion channels, which improves neuronal hemostasis and increases the resistance of cells to nerve damage occurring during seizure episodes.

Another positive aspect of using KD in epilepsy is the fact that the body's antioxidant defense is improved through increased production of glutathione. Reactive oxygen species (ROS) produced during an epileptic seizure, which can potentially damage nerve cells, are then more effectively neutralized [23,24]. What's more, the use of KD contributes to the increase in the synthesis of gamma-aminobutyric acid (GABA), which is a neurotransmitter that inhibits the activity of nerve cells. It is also suspected that it has a significant influence on the anticonvulsant effect of KD [25].

Many mechanisms of action of ketones on neurons are not known yet and are subjected to numerous studies *in vivo* as well as *in vitro*. For example, acetoacetate and acetone have been shown to protect against convulsions in mice susceptible to sound-induced convulsions (the

Frings model). It was later found that acetone increased the seizure threshold in rats in a number of models of seizure induction simulating tonic-clonic seizures and absence seizures. Based on this, it can be cautiously concluded that acetone has an anti-seizure profile, noticeable as well in patients on a ketogenic diet [26].

Side effects and contraindications to the use of KD

The study, which involved 472 children and adolescents (up to 18 years of age) with drug-resistant epilepsy, also focused on the side effects of this therapy. The most common ailments were gastrointestinal disorders, i.e. diarrhea, constipation and vomiting. They concerned 30% of the respondents. Other, quite frequent ailments reported by patients included: respiratory tract infections, abdominal pain, anorexia or hyperammonemic encephalopathy, lethargy, weight loss, gastroesophageal reflux or lack of appetite [27,28]. Another review mentions less common side effects, which include nutrient deficiencies, possible kidney stones, increased infections, and an increased susceptibility to bone fractures. One case was cited where the complication was protein-losing enteropathy, edema and hypoalbuminemia. Reducing the ratio of fat to carbohydrate in the diet resulted in regression of symptoms [29]. Due to the change of the basic energy source from glucose to lipids, the ketogenic diet is contraindicated in cases of lipid metabolism disorders, i.e. their transport and oxidation, pyruvate carboxylase deficiency or porphyria [30,31].

Findings

There are publications describing the use of various types of diets in the treatment of drug-resistant epilepsy, and these are: Atkins diet, low glycemic index diet, medium-chain triglycerides and classic ketogenic diet, to which we will devote the most attention. Doctors usually recommend a ketogenic diet for children. In the case of adults, better results are obtained using the Atkins diet. It is important that pharmacological treatment is continued during dietary treatment, which may be modified or remain the same. Studies show that the ketogenic diet reduces or even stops epileptic seizures in situations where it was not possible to control their treatment by AEDs only. In more than half of the children who were introduced to the ketogenic diet, a 50% reduction in epileptic seizures was observed. In 10-15% complete remission of seizures was observed [32]. The effects of using KD can be noticed up to 3 months after its introduction. Among the observed positive effects are alleviation of symptoms, improvement in behavior, concentration, attention, quality of life

and sleep, and cognitive abilities. It is also important to supervise the level of nutrients, supplementation of vitamins and trace elements. In children, it is important to ensure an adequate supply of protein to ensure proper growth and development [33]. It is relevant to encourage the patient and family to continue the diet for a minimum 3 months so that it can be reliably assessed whether the diet has an impact on a particular patient.

Regardless of the effectiveness of the diet, many patients discontinue it due to difficulties in complying with its restrictive recommendations and due to poor taste [34]. One of the meta-analyses included 16 studies and a total of 338 patients, both children and adults with symptomatic focal and generalized idiopathic epilepsy who have had at least 2 or 3 seizures attacks per month, using one or two antiepileptic drugs. For the period from 3 to 36 months, they received KD and its modifications as a supplement to pharmacological treatment. In these trials, the proportion of patients who showed more than a half of reduction in seizures ranged from 20 to 70%, and the proportion of patients who had seizure relief ranged from 7 to 30%. The discontinuation rate ranged from 12.5 to 82% of patients. Side effects were mild and the most common were weight loss and dyslipidemia. This meta-analysis showed that the use of a ketogenic diet in adults with drug-resistant epilepsy is an effective and promising treatment [35]. In 2022, another study was conducted on 160 pediatric patients who were on a ketogenic diet and the effects were observed at 3,6,12,24 months after its introduction. Non-occurrence seizures were noted after 3 months in 13.7% of children, after 6 months in 12.5%, after 12 months in 14.4% and after 24 months in 10.6%. A reduction in seizure frequency of at least 50% was observed in 41.9% of children after 3 months, 37.5% after 6 months, 28.7% after 12 months and 16.2% after 24 months [36]. Another meta-analysis conducted in 2022 found that children with epilepsy on a ketogenic diet are 5.6 times more likely to reduce their seizure frequency by at least 50% [37]. The results of the next meta-analysis show that 33% of the children studied had a complete remission of epileptic seizures, and 59% of the children studied had a seizure reduction of at least 50% [34,38]. One of the studies included 91 children of different ages with drug-resistant epilepsy. Patients maintained a ketogenic diet for at least 12 months. After this time, 35.2% of patients remained seizure-free and 70.3% of children achieved a seizure frequency reduction of at least 50% [39]. The latest review analyzed the results of 11 studies on sick children and adults (778 patients in total) using classical KD and MAD. The effectiveness was tested after three months and was as follows: In KD, seizure-free rates reached 55%, and seizure reduction rates reached as high as 85%. In

MAD in children, seizure absence rates were up to 25%, and seizure reduction rates reached up to 60% [40].

SUMMARY

Drug-resistant epilepsy is a major challenge for today neurology. Despite modern therapies, one in three epilepsy patients consistently experience symptoms. Each seizure is detrimental to the functioning of the central nervous system and negatively affects neurons, so new alternative therapies are persistently sought. One of them is chronic use of the ketogenic diet. It is commonly known and associated with the treatment of obesity, but it turns out that there are more benefits from the matabolism changes that occur in the body thanks to it. Recent data show that ketones from the ketogenic diet are not only energy substrates, but also have the effect of reducing the frequency of epileptic seizures in children and adults by producing particular neurotransmitters, helping neutralize oxygen free radicals or supporting the functioning of ion channels. Unfortunately, as of today, it is impossible to put forward a final thesis, due to the difficulties in conducting research (number of cases, age groups, assessment of reliability in dieting, etc.).

However, based on the above data, it can be concluded that in many cases the number of seizures decreased and this concerned all age groups. The above data show that in many cases, the inclusion of a ketogenic diet had a positive effect on the health of patients suffering from drug-resistant epilepsy and often became the last effective lifeline improving the quality of life. Undoubtedly, long-term side effects require further research and must be managed by an interdisciplinary team. We must remember that the ketogenic diet has many contraindications and, despite its positive effect on the nervous system, it may disturb the functioning of other organs and systems. There are still many unknowns ahead of the researchers, but the information gathered so far seems to be promising.

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Authors' contributions:

Conceptualization, N.D., M.B., J.B. and H.P-S; Methodology, N.D., A.B and J.B.; Software, N.D., M.K., and M.B.; Check, M.B. and N.D.; Formal Analysis, N.D., M.K. and A.B.; Investigation, J.B., A.B. and M.B.; Resources, A.B., N.D. and M.K.; Data Curation, M.K. and

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