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The role of the ketogenic diet in the treatment of epilepsy

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Abstract

Introduction:

Epilepsy is a prevalent neurological condition that continues to pose therapeutic challenges. Despite the availability of various antiepileptic medications, up to one-third of patients still experience insufficient control of their seizures. One approach to managing epilepsy, particularly in drug-resistant cases, is the ketogenic diet. This diet, along with its variations, has shown effectiveness in reducing seizures across all age groups, with additional improvements in behavior. However, despite numerous studies, the exact mechanisms behind its therapeutic effects and potential risks to the body remain unclear. This review of the current literature outlines the fundamental principles and variations of the ketogenic diet, evaluates its safety and effectiveness in treating epilepsy, and explores the possible mechanisms underlying its success.

Materials and methods:

This article is based on the literature found in the PubMed database with the use of keywords like: "drug resistance epilepsy", "ketogenic diet", "epilepsy treatment".

Conclusion:

The ketogenic diet is an effective treatment for epilepsy, especially drug-resistant forms. It reduces the number of seizures and it also has a positive effect on patients' sleep and cognitive functions. Despite many years of using the diet and observing its effects we still do not fully understand its mechanisms of action.

key words: epilepsy; ketogenic diet; modified Atkins diet; low glycemic index; drug-resistance epilepsy

1. Introduction

Epilepsy is a neurological disorder affecting approximately 65 million people worldwide. It cannot be effectively controlled with pharmacological treatments in one-third of patients. According to the ILAE, drug-resistant epilepsy (DRE) occurs when sustained seizure freedom is not achieved despite the use of two appropriately selected and properly administered antiepileptic drugs, either in monotherapy or combination therapy.[1] In patients with DRE alternative treatments such as the ketogenic diet, surgical procedures or vagus nerve stimulation can be considered. The first reports of fasting's influence on seizure control date back to the time of Hippocrates. The classic ketogenic diet was introduced as a common therapy for epilepsy seizures in the 1920s. Than it was observed that in patients who were fasting or following a low-carbohydrate diet ketone bodies appeared in the body and it had a positive effect on patients suffering from epilepsy.[2]

After the introduction and dissemination of antiepileptic drugs the diet was abandoned mainly due to its poor taste and high abandonment rate. In the face of observed drug resistance despite the development of new anti-epileptic drugs it was popularized again by Ch. Abrahams as an effective treatment for seizures in the 1990s.[3]

2. What is the ketogenic diet?

The ketogenic diet consists of high-fat, low-carbohydrate and medium-protein products.[2] It is planned individually for each patient. Its appearance may vary and depends on the guidelines in force in a given country. [4] Restrictive proportions in the consumption of carbohydrates, proteins and fats leads to the state of ketosis in the body (to increased production of substances such as β-hydroxybutyrate, acetoacetate and acetone - ketone bodies). Glucose is not an energy substrate for the body's cells due to the low supply of carbohydrates and the source of energy are ketone bodies produced from fats.[5]

3. Biochemistry of ketosis

Limiting carbohydrate intake reduces glucose levels and reduces insulin secretion in the body. The glucose reserves stored in the liver in the form of glycogen are activated but these reserves are depleted after about 3-4 days.[6] Then the body begins to produce glucose in the process of gluconeogenesis. The substrates for this are: alanine, glutamine, glycerol and lactic acid. Free fatty acids (FFA) from adipose tissue and diet become the source of energy when gluconeogenesis is not able to meet the body's energy needs. Fatty acids are oxidized in the liver and the product of this reaction are ketone bodies - a source of energy for the body's cells. Low insulin levels in the blood cause an increase in FFA uptake by liver cells. They are transported to the mitochondria using carnitine palmitoyltransferase where they are oxidized to Acetyl-CoA in the process of beta oxidation. Low glucose concentration induces a reaction in which acetoacetate (ACA) is formed from 2 Acetyl-CoA molecules. ACA can spontaneously convert to acetone or to β-hydroxybutyrate (BHB). All these 3 substances (called ketone bodies) accumulate in the body during long-term exposure to the ketogenic diet. [3] Brain cells during fasting (or lack of glucose) can produce energy from ketone bodies. This phenomenon is metabolic flexibility.[2] They are transported to the brain via the monocarboxylic transporter-1 (MCT-1) where they are used to produce ATP. Ketone bodies produce more ATP molecules compared to glucose. That's why it is an effective substrate during a caloric deficit.[3] Blood or urine ketone levels are used to monitor patients' adherence to dietary recommendations but there is no clear evidence in the available literature that the number of seizures correlates with urine, breath or serum ketone levels. Publications have reported that there may be a threshold concentration of ketones required to achieve seizure control and that serum ketone levels correlate better with seizure control than urine ketone concentrations.[7]

4. Modifications of the ketogenic diet and their efficacy

The classic form of the ketogenic diet (long-chain triglyceride ketogenic diet (LCT KD)) has gained several modifications over the period of its use: modified Atkins diet, medium-chain triglyceride diet, low glycemic index diet. The level of compliance has increased and some of the side effects have been reduced due to them. It did not significantly affect its effectiveness at the same time.[8]

4a.long-chain triglyceride ketogenic diet (LCT KD)

It presupposes a specific ratio of grams of consumed fats to the total number of grams of protein and carbohydrates (usually 4:1). In this situation about 90% of energy comes from fat. The classic ketogenic diet limits the number of calories consumed to 90% of the patient's daily requirement. The diet can be introduced in 2 ways. The first method involves fasting for several hours (12-72 hours). Followed by the introduction of meals with a gradual increase in their caloric content by one-third until the desired caloric intake is reached. An alternative method which helps avoid hospitalization due to some side effects of fasting (acidosis, weight loss, hypoglycemia) is to progressively increase the ratio of grams of fat consumed to grams of carbohydrates and protein consumed without limiting the number of calories. Initially the ratio is 1:1, then 2:1, 3:1, and finally 4:1.[9] The classic form of the ketogenic diet can be difficult to maintain due to the difficulties in its preparation and the limited taste appeal associated with the low carbohydrate intake.[8] In a cohort study evaluating changes in EEG during wakefulness in pediatric patients on the ketogenic diet (KD) compared to the period before starting the KD, it was shown that after one month, most of them had a reduction in seizure discharges, though the degree of reduction varied between individuals. The reasons for the differences in response to treatment could not be identified. Furthermore, it was observed that those who had a significant reduction in discharges after one month had up to a six-fold greater chance of clinical improvement after three months compared to those who did not show a significant reduction in discharges after the first month. The authors noted that this may encourage patients who have not yet observed clinical improvement after the first month to continue the diet. [10] A meta-analysis of studies on the efficacy of the ketogenic diet (KD) in the treatment of epilepsy conducted in the pediatric population showed a seizure reduction of at least 50% in 48.31% of patients. Patients on the KD were 5.6 times more likely to achieve a >50% reduction in seizures compared to the control group.[11]

4b.Modified Atkins Diet (MAD)

It assumes that the patient consumes approximately 65% of their calories in the form of fats. Initially carbohydrate intake should be limited to 15g/day for adults and 10g/day for children and it can be increased to a maximum of 20-25g/day depending on the level of seizure control. In the Modified Atkins Diet (MAD), there is no need to restrict the number of grams of protein or calories consumed. There is a lot of publications confirm an efficacy of MAD in pediatric population.[4] In an observation comparing the efficacy of the ketogenic diet (KD) to the Modified Atkins Diet (MAD) in treating epilepsy, a greater tendency for seizure reduction was noted with KD, but this did not reach statistical significance. Additionally, this relationship was not observed after adjusting the groups for age (the average age in the MAD group was higher than in the KD group). Considering the overall observations it appears that the efficacy of MAD and KD is comparable.[12] In a randomized controlled trial conducted on 102 children with drug-resistant epilepsy (DRE) patients following the Modified Atkins Diet (MAD) for 3 months had a significant reduction in seizure frequency compared to the control group (the median number of seizures in the diet group was 37.3% of the baseline value vs. 100% of the baseline value in the control group).[13] Less data is available regarding older age groups. However, in a prospective study evaluating the safety, efficacy, and tolerance of the Modified Atkins Diet in adolescents and adults with drug-resistant epilepsy it was shown to be effective in controlling seizures, improving patients' quality of life and was well tolerated.[14]

4c. Medium-chain triglyceride diet (MCT)

Assume that the consumption of medium-chain triglycerides (MCTs) results in the production of more ketones per gram compared to long-chain triglycerides, which are the basis of the classic ketogenic diet. This allows for an increase in the amount of carbohydrates and protein consumed in the diet. This positively affects the taste of the diet and improves adherence. In the MCT diet approximately 60% of the kilocalories come from fats.[4][9] A study comparing the classic diet and MCTs in the effectiveness of treatment in drug-resistant epilepsy did not show the advantage of either of them. Ketone concentrations in the body were significantly higher during the classic diet. It emphasizes the complexity of the relationship between ketosis and seizure control. [15]

4d. Low Glycemic Index System

It involves the consumption of carbohydrates with a low glycemic index (<50) in order to maintain a stable glycemic level in the body.[4] A retrospective study was conducted among children who had a diet with a total carbohydrate restriction of 40-60g per day (these carbohydrates had a low glycemic index). A reduction in the number of seizures by more than 50% compared to baseline was observed in 42%, 50%, 54%, 64%, and 66% of the participants (evaluated at 1, 3, 6, 9, and 12 months after starting the LGIT). It demonstrates the effectiveness of this type of diet with a low incidence of adverse effects. [7]

Systematic review and network meta-analysis of PubMed publications from 2023 showed that children with DRE were about 50% more likely to reduce seizures with different types of ketogenic diets (KD, MAD, low index, short-chain) than with standard therapy. The frequency of drop-out was higher especially with KD and MAD.[16]

5.Safety of ketogenic diet

The ketogenic diet should be started with the control for possible side effects. For these reasons it is important to be cared for by a therapeutic team consisting of a doctor and a dietician who will supervise the patient. We can divide them according to the time of occurrence [4] and because of the arrangement on which they act. It has been reported in more than 40 different categories of adverse reactions until now. The most common of them were gastrointestinal, kidney, cardiovascular and osteoarticular complaints. It is worth adding that the stricter diet more often causes side effects. [2] Most centers prefer to start the diet in hospital conditions. It is also possible at home. It has been noted that outpatient introduction of the diet may have a positive effect on adherence. [17] The ketogenic diet is absolutely contraindicated in the case of: primary carnitine deficiency, carnitine palmitoyltransferase (CPT) I or II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency, porphyria. [18]

Table 1: The early and late side effects of the ketogenic diet.[4]

appear shortly after the implementation of the diet	**appear after 3 months after the implementation of the diet**
acidosis	hyperlipidemia
GERD	constipation
hypoglycemia	growth inhibition in children and adolescents
nausea	vitamins and minerals deficiency
vomiting	nephrolithiasis
diarrhoea	

Table 2: Summary of the most common side effects of the ketogenic diet.[2][9][19]

category	side effects	comment
gastrointestinal	constipation	The incidence increases with exposure time. Symptom relief can be achieved by using enemas, stool softeners, limiting the intake of dietary fiber. [19]
	gastrointestinal disorders, vomiting	In the population of children from Thailand on a ketogenic diet of medium-chain triglycerides there was observed even 25% incidence of vomiting. We can use anti-emetic agents and rehydration in treatment. Correcting the ratio of macronutrients in the diet may be helpful. [2]
	hepatitis, gallbladder stones, pancreatitis	
renal	nephrolithiasis, chronic kidney disease, ketoacidosis	It is recommended to include potassium citrate (2mmol/kg/d) in patients starting a ketogenic diet at the same time. This supplementation prevents the formation of kidney stones, can reduce acidosis and

		limit the decline in bone mineral density by alkalizing urine.[2] Its significant side effect is constipation.[19]
height	reduced growth rate in children	Studies have reported conflicting results on the effect of diet on stunted growth. More often noticed in dietary regimens that limit the number of calories consumed. Mineral supplementation should be used. [2] The growth rate should be monitored. [19]
bones	decrease bone mineral density	The studies are not consistent. There was observed a decrease in bone mineralization of the lumbar spine. It deepened with each year of using the KD diet. Per contra, in some studies there were no significant changes. A DEXA scan can be performed for control purposes and the supplementation should be considered. [19]
cardiovascular	dyslipidemia, long QTc syndrome,, cardiomyopathy	In some patients the use of the ketogenic diet (KD) resulted in hyperlipidemia and hypercholesterolemia, but cholesterol levels were only slightly elevated (201 mg/dL). [2] Magnesium and selenium deficiencies seem to be responsible for long QT syndrome and the occurrence of cardiomyopathy.[9] It is important to monitor the lipid profile during the ketogenic diet and it may be advisable to consider less restrictive forms of the diet to reduce the impact of micronutrient deficiencies.[2][19]

6.Supposed mechanism in epileptic seizures control

There are many potential mechanisms of therapeutic action of KD in epilepsy therapy. It is not known exactly which of them are actually important. [3]

6a.Impact on ion channels and neurotransmitter synthesis

Low blood glucose levels in patients with KD lead to a decrease in pyruvate concentration. This results in the opening of ATP-dependent potassium channels and hyperpolarization of neurons. Ketone bodies may have a direct neuroprotective effect also. Acetone induces hyperpolarization

of neurons by activating double-pore ion channels for potassium ions (K2P channels). Both of these mechanisms prevent excessive neuronal discharges by reducing excitability. [20] It has been observed that MCTs cause an increase in the plasma concentration of decanoic acid, which is an antagonist of the AMPA receptor (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor).[21] The blockade of AMPA by decanoic acid occurs through a non-competitive mechanism and leads to direct inhibition of neurotransmission in the central nervous system.[22] The use of a ketogenic diet may affect the synthesis of gamma-aminobutyric acid (GABA) and glutamate. Glutamate in nerve cells is converted into glutamine. Then glutamine is transformed into GABA or aspartate. The synthesis of aspartate occurs in the presence of oxaloacetate. The concentration of aspartate decreases because oxaloacetate is increasingly utilized for energy production in the tricarboxylic acid cycle (TCA) (a phenomenon typical to KD). Decrease of oxaloacetate's concentration causes the synthesis of GABA (inhibitory neurotransmitter) increases.[22] The ketogenic diet increases the production of adenosine by enhancing the metabolism of astrocytes also. Adenosine reduces the excitability of nerve cells by binding to A1 adenosine receptors and decreases the release of glutamate.[9]

6b. Impact on mitochondrial stabilization

The ketogenic diet reduces the production of reactive oxygen species (ROS) which can damage mitochondria. At the same time, it improves the function of these structures by increasing metabolic efficiency. Mitochondrial stabilization is another proposed mechanism for reducing the number of seizures.[9]

6c. Anti-inflammatory effect

BHB (a metabolite produced during the use of KD) has anti-inflammatory properties which protect nerve cells against damage. Its high concentration reduces the synthesis of the NRLP-1 inflasome which is responsible for inflammatory signaling in nerve cells. [23]

6d. Impact on the intestinal microbiota

Disturbances in the composition of the gut microbiota are observed in patients with epilepsy. In this situation, the synthesis of certain neurotransmitters (including GABA) may be impaired. The use of the ketogenic diet (KD) has a beneficial effect on the altered microbiome. It increases

GABA synthesis and the GABA/glutamate ratio. The result of this mechanism is an anticonvulsant effect.[21]

6e.Impact on sleep and cognitive functions

Patients suffering from epilepsy often experience sleep disorders. They can create a "vicious cycle" by increasing the frequency of seizures and making epilepsy more difficult to treat. Sleep deprivation lowers the seizure threshold and also affects the overall functioning of patients (including behavior, learning, and mood).[24] Sleep disorders in people with epilepsy may be caused by poor sleep hygiene, the use of antiepileptic drugs and changes resulting from alterations in sleep structure in individuals with epilepsy. [9] Studies have shown that people with epilepsy experience a reduction in total sleep time, shortening of the REM phase and an increased number of phase shifts. Additionally, patients with drug-resistant epilepsy have prolonged slow-wave sleep (SWS) and shortened stage 2 sleep.[25] The use of the ketogenic diet has a positive effect on improving sleep pattern. [9] A study analyzing sleep in children with drug-resistant epilepsy during the use of the ketogenic diet observed a reduction in total sleep time and an improvement in sleep quality. This simultaneously enhanced their quality of life (QOL).[26] Furthermore, it has been shown that the ketogenic diet positively affects attention and concentration, cognitive abilities, patient alertness and interpersonal interactions. It should be noted that a longer duration of exposure to the diet increased the degree of clinical improvement.[27][28] The improvement was not associated with a reduction in the number of seizures and there was no relationship with the amount of anti-epileptic drugs taken.[28]

Summary:

A lot of observations and studies confirm the effectiveness of the ketogenic diet in the treatment of epilepsy. Patients experience a reduction in seizure frequency, improvements in sleep quality and enhanced cognitive abilities. Further research is needed to determine which mechanisms are truly significant and which patients may benefit the most from dietary therapy. It also seems that the diet should not be considered as last-resort treatment but rather an equivalent component of the therapeutic pathway.

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