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The use of ketogenic diet in therapy of drug-resistant epilepsies – current state of knowledge

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Abstract

Introduction and Objective. Epilepsy is a neurological disorder where a desynchronization occurs in the discharge of neurons of specific brain areas. Clinically, this manifests as epileptic seizures with possible disturbances of consciousness. Therapy of epilepsy is based on pharmacotherapy, but in cases of drug resistance, alternative methods, such as ketogenic diet (KD) should be explored. The aim of this review is to present the current state of knowledge concerning the use of KD in epilepsy and the clinical results of such therapy.

Review Methods. PubMed, PubMed Central and Google Scholar databases were searched using key words related to epilepsy, ketogenic diet, metabolic mechanisms of ketosis and antiepileptic effects of ketone bodies. Articles and book sections in English were searched and reviewed. Articles were selected after analyzing abstracts and those that matched and described the topic in a proper way were used. The types of articles included prospective studies, retrospective studies, reviews and meta-analyses.

Brief description of the state of knowledge. From the initial search, 20 articles strictly concerning the KD mechanisms of action, its antiepileptic effects and the results of the therapy conducted were retrieved for final analysis. Available data provide the information specifically on the definition of KD, adverse effects, anti-seizure mechanisms and therapy results mainly from recent years. KD is currently being used as an alternative therapy in drug-resistant epilepsies. The reduction in seizures after its use averages about 50%, and some studies have shown up to 90% effectiveness in seizure reduction.

Summary. Understanding the mechanisms of brain metabolism allowed the use of KD in the treatment of epilepsy and other neuropsychiatric diseases. The results of the therapy appear to be satisfactory and provide hope for future epilepsy therapy.

Key words

neurotransmitters, ketogenic diet, ketone bodies, epilepsy, therapy effectiveness

INTRODUCTION

Definition and epidemiology. Epilepsy is a widespread neurological disorder affecting more than 70 million people worldwide. A high percentage of epilepsy patients are to be found in developing countries [1]. For this reason, many patients do not receive treatment due to the economic situation, despite the fact that proper therapy significantly reduces the risk of complications, disability or death [2]. Epilepsy can affect people of all ages, regardless of gender, race, social status and geographic location [3]. The median incidence of acute symptomatic seizures is estimated at 29–39 cases for every 100,000 people per year. These seizures are most commonly seen in infants and the elderly and can be triggered by a variety of factors, such as fever, traumatic brain injury (TBI), cerebrovascular disease, interruption of therapy, infections or metabolic disorders [4]. Fiest et al. found that the overall rate of new cases of epilepsy per 100,000 person/years was 61.4 (95% confidence interval (CI) 50.7–74.4). The incidence of epilepsy was higher in low/middle-income countries compared to high-income countries, with rates of 139.0 (95% CI 69.4–278.2) and 48.9 (95% CI 39.0–61.1), respectively. In addition, the incidence of epilepsy was slightly higher in men than in women [5]. In children, the highest incidence of epilepsy is observed in the first year of life, but by the age of 10, the incidence of epilepsy tends to decrease to levels similar to adults [6].

Causes and clinical symptoms. Proper diagnosis of epilepsy is essential for effective treatment as different types of epilepsy require different approaches [7]. Epilepsy is classified based on the type of seizure and symptom complex, with the cause and comorbidities identified. The causes of epilepsy can be divided into several categories, such as genetic, toxic, structural, metabolic, infectious or unknown (Tab. 1) [8].

The causes of epilepsy vary by age group. In children, the most common causes of epileptic seizures are genetic defects, perinatal injuries and malformations of the cerebral cortex, while cumulative brain damage is most common in the elderly [9, 10]. In about 50% of cases, the cause of seizures is unknown [11]. Seizures appear when abnormally synchronized neuronal discharge occurs in a specific area of the brain [9]. Provoked seizures (caused by the factors mentioned earlier) have a higher mortality rate within the first 30 days compared to unprovoked seizures. Mortality is highest in elderly patients and depends on the cause rather

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Table 1. Causes of epileptic seizures. Based on [8,12]

Metabolic	hypo/hyperglycemia, hypo/hypernatraemia, hypocalcaemia, uraemia, cerebral hypoxia
Toxic	Alcohol intoxication, drug intoxication (e.g. barbiturates, benzodiazepines), withdrawal syndrome (e.g. alcohol, cocaine, amphetamine); CO intoxication
Trauma	traumatic brain injury, concussion, stroke, intracerebral haemorrhage, subdural haematoma, iatrogenic trauma
Structural	CNS tumour, cerebral venous thrombosis, posterior reversible encephalopathy syndrome (PRES), vascular malformations
Infectious	tuberculosis, HIV, cerebral malaria, cerebral toxoplasmosis, CMV, Zika virus, neurocysticercosis, subacute sclerosing panencephalitis (SSPE)
Genetic	mutations in KCNQ2, KCNQ3, SCN1A genes.
Immunological	Auto-immune CNS inflammations (encephalopathies with the production of antibodies against NMDA receptors and against LGI1 receptors)
Unknown	patients who have epileptic seizures – but it has not been possible to determine their cause due to the unavailability of diagnostic methods

than the seizures themselves [12]. Epileptic seizures can also be the direct result of structural damage to the brain. Focal Cortical Dysplasia (FCD) is a group of disorders where the architecture of the cerebral cortex is damaged due to abnormal cell proliferation. Hippocampal sclerosis with associated gliosis is also a condition often associated with chronic epilepsy. Porencephaly is associated with the formation of cysts that damage the cerebral cortex due to infarct lesions. Rasmussen's inflammation is a disorder that occurs mainly in children and is characterized by hemispheric atrophy, severe focal epilepsy, mental retardation and hemiparesis. In addition, epilepsy can be caused by neoplastic lesions such as ganglioneuromas, dysembroplastic neuroepithelial tumours, pleomorphic cholesteatoma, angiocentric gliomas or cavernous angiomas [13]. The main types of epileptic seizures are atonic, myoclonic, absence (formerly petit-mal) and generalized tonic-clonic (GTC) (formerly grand-mal). Atonic seizures usually result in collapse due to loss of muscle tone, myoclonic seizures present sudden movements with no obvious disturbance of consciousness, absence seizures involve unresponsiveness to external stimuli and staring at surrounding points, while GTC seizures present convulsive movements and stiffening of the limbs with disturbance of consciousness present. In addition, seizures can be classified as either generalized or focal, with the focality of symptoms tending to apply to myoclonic seizures [14]. It is worth mentioning at this point one of the most serious complications that relates to GTC seizures. Sudden unexpected death in epilepsy (SUDEP) is the unexpected and non-traumatic death of a person with epilepsy whose autopsy did not reveal a toxicological or anatomical cause of death [15]. SUDEP is the leading cause of death in some epilepsy populations and is the second leading neurological cause of the total number of years of potential life lost after stroke [16]. SUDEP often follows a tonic-clonic seizure that occurs during the hours of sleep [17].

Epileptic syndromes. Epileptic seizures, along with the presence of certain clinical symptoms, can be classified as a specific epileptic syndrome.

Lennox-Gastaut Syndrome (LGS) is a severe form of epilepsy characterized by multiple types of seizures, a specific EEG recording and intellectual disability. As an epileptic encephalopathy, the syndrome can result in structural brain damage and cognitive and developmental problems [18]. The underlying causes of LGS are often genetic, structural or metabolic, and can be identified in up to 75% of patients. However, in some cases, the cause remains unknown. Treatment of LGS is difficult, and the main goal is to reduce the frequency and severity of seizures. Long-term treatment results are not satisfactory [19, 20].

West Syndrome (WS) is a complex disorder with the classic triad of symptoms: infantile spasms, hypsarrhythmias and delayed child development. In addition to these symptoms, other clinical and electroencephalographic features are present in affected children, expanding the spectrum of disorders [21].

Ohtahara Syndrome (OS) is a rare and severe form of epilepsy that manifests during the first few weeks or months of life with incurable epileptic seizures [22]. Infants experience focal or generalized tonic spasms that can occur hundreds of times a day [23]. Prognosis is generally poor, with many infants dying in infancy and survivors developing severe or profound psychomotor retardation [24]. OS is associated with various genetic abnormalities (e.g., STXBP1, KCNQ2, NaV1.2 gene, SLC25A22 or KCNT1 genes) impairing the function of ion channels or mitochondrial transport [25–27].

Dravet Syndrome (DS) is also caused by a genetic defect (SCN1A). It is not entirely clear how often people with this mutation develop Dravet syndrome and how severe the course of the disease is expected to be [28, 29]. The cited syndromes are most often refractory to treatment with classical pharmacotherapy, and in such cases surgical interventions become helpful. However, if there are contraindications to radical treatment, alternative options, such as medical marijuana therapies or the use of a ketogenic diet, are considered.

STATE OF KNOWLEDGE

Classical epilepsy therapy. Due to the multiplicity of possible clinical manifestations of epilepsy, the many varieties of seizures and the differences in the etiology of the disease in different patients, there are many therapeutic options with an individualized approach to the patient. Currently, the most common forms of treatment are pharmacotherapy and/or neurosurgical intervention [30, 31]. Alternative methods include: ketogenic diet, vagus nerve stimulation, or deep brain stimulation [31] When choosing a therapeutic path, the physician should consider the patient's personal factors (age, gender, lifestyle, occupational activity), etiology of the disease, and type of seizures. The patient should also be informed about the possible side-effects of a particular drug or the risks associated with the treatment, and the final decision on the further direction of treatment should be made with the patient's consent and approval [30].

Drug-resistant epilepsy. It is estimated that in a population of patients not previously taking antiepileptic drugs with a history of newly diagnosed epilepsy, seizure control after first-line drug use is achieved in 50% of cases. The use of a second drug, on the other hand, achieves control in 65% of patients. Unfortunately, only 4% of patients manage to achieve control after using a third drug [3]. This implies

that about 1/3 of patients have seizures that will not be pharmacologically controllable and will require an alternative form of therapy [32].

Recent decades have seen rapid advances in clinical neurology, and many new anticonvulsants with more favourable side effect profiles and better tolerated by patients have been introduced to the market, while their efficacy has not yet been significantly improved [33]. According to the International League Against Epilepsy (ILAE) definition, drug-resistant epilepsy is diagnosed when two consecutive attempts at drug interventions in monotherapy or add-on therapy (well-tolerated, properly selected and appropriately used), fail to achieve sustained and complete seizure control [34]. In such a situation, neurosurgical intervention is the most commonly recommended further treatment.

Pharmacotherapy. The use of antiepileptic drugs is aimed at controlling seizures and improving the patient's quality of life. Antiepileptic drugs act symptomatically, not causally. They are effective in two-thirds of patients, but the response can vary depending on the patient, the type of epileptic syndrome, etiology of the disease and the frequency of seizures before treatment [35]. When deciding whether to initiate antiepileptic treatment, the risks and benefits, as well as the preferences of the patient and family, should be carefully considered. Treatment is usually recommended after a diagnosis of epilepsy, but may also be necessary after a single seizure if the risk of recurrence is high and may cause harm or social consequences. On the other hand, treatment may not be necessary for mild forms of epilepsy, such as patients with infrequent and non-conscious focal seizures [36]. Treatment usually begins with a single antiepileptic drug at a low dose, which is gradually increased to the lowest effective maintenance dose to minimize adverse effects [37]. Approximately half of patients experience seizure freedom after the first drug [38]. There is no single antiepileptic drug suitable for all patients. First-line medications for epilepsy remain older drugs, such as carbamazepine and valproic acid; for focal epilepsy, carbamazepine, lamotrigine and oxcarbazepine proved more effective than topiramate and gabapentin, with lamotrigine slightly better than carbamazepine due to fewer side-effects. Valproic acid is more effective than lamotrigine and topiramate for generalized and unclassified epilepsy [39]. Other studies comparing controlled-release carbamazepine with other second-generation antiepileptic drugs, such as levetiracetam, zonisamide and lacosamide, have shown no significant differences in the efficacy or tolerability of the afore-mentioned drugs [40–42]. Valproic acid is not recommended for women of childbearing age due to the higher risk of anatomical teratogenesis and impaired cognitive development and autism in the offspring [43]. For patients whose seizures persist despite increasing the dose of the first antiepileptic drug to the maximum tolerated optimal dose, the diagnosis should be re-evaluated and a new treatment introduced [44].

Surgical treatment. Surgery involves the resection, or less commonly, the destruction of brain tissue that is the source of the excitation. Surgery is a highly effective treatment option for some patients with drug-resistant epilepsy. Patients undergo a series of examinations, EEG, MRI, PET and neuropsychological tests before surgery. These activities help determine the minimum amount of cortex that needs to be removed in order for the treatment to be effective and free the patient from the occurrence of seizures, as well as reduce the risk of post-operative complications. In some cases, an intracranial EEG may be necessary. The effectiveness of the procedure depends on many factors, such as the type of epilepsy, correctly performed pre-operative tests, epilepsy pathology, and the area of resection [45]. Ramos-Perdigués S. et al. describe a frequent improvement in patients' overall mental status in anxiety disorders, depression and other related behavioural problems occurring after undergoing surgical treatment. On the other hand, patients with drug-resistant epilepsy who do not undergo surgery tend to have an increase in the above symptoms [46].

In conclusion, surgical interventions are carried out for more complex cases of epilepsy. The results of treatment are very positive. This includes not only a reduction in seizure frequency, but also an improvement in quality of life [47].

The ketogenic diet. The effect of fasting on seizure control in epilepsy had already been observed in ancient times. In the 1920s, it was discovered that a diet consisting mainly of fats and low in carbohydrates could successfully mimic the effects of fasting in controlling epileptic seizures. This diet was later called the ketogenic diet (KD), and the reasons for its positive effects on patients with epilepsy were sought primarily in the increased production of ketone bodies: beta-hydroxybutyric acid (BHB), acetylacetic acid (acetyloacetate) and acetone in the liver. Despite the early success of the ketogenic diet, the discovery of antiepileptic drugs (AEDs) in the 1940s pushed research into its therapeutic use into the background. However, by the end of the 20th century, interest in the clinical use of the ketogenic diet had grown significantly, and over the past three decades it has become a generally accepted therapeutic option for the treatment of drug-resistant epilepsy, and a wide range of other neurological diseases, and its positive effects have been confirmed by numerous studies [48]. The basis of the ketogenic diet is a very high proportion of fats and a low proportion of carbohydrates in the macronutrient composition. Optimally, carbohydrates should cover less than 10% of the patient's daily energy requirements. This causes changes in metabolism, forcing cells to use ketone bodies instead of glucose as the main energy substrates. A ketogenic diet provides a sufficient supply of protein for growth and development. Energy comes mainly from fats supplied with food and from the use of the body's fat reserves. The ketogenic diet allows about 90% of daily caloric needs to be covered by fats, 6% by proteins and 4% by carbohydrates [49]. Ordinarily, the ketogenic diet was considered the 'gold standard' in the treatment of metabolic disorders, but now studies are systematically being published confirming its positive effects in many neurological diseases. For example, 70% of patients with West syndrome show clinical improvement compared to an average of 50% with standard treatment of the condition [50].

Variations of KD

Classic Ketogenic Diet (CKD) is calculated according to the Glucose-Ketone Index (GKI). GKI is the ratio of fats to carbohydrates and proteins in grams. The most common ratios used in practice are 3:1 or 4:1, meaning that for every 3–4g of fat there is a total of 1g of protein and carbohydrate. The caloric supply is generally limited to 80–90% of daily

requirements, taking age into account. Fluid intake is also limited to about 90% of daily requirements, but this rule is used due to the historical use of the diet rather than scientific evidence [51].

was originally proposed at John Hopkins Hospital in Baltimore, Maryland, USA, in 2003. Therapy with this diet is conducted in an outpatient setting and does not require fasting, caloric or fluid restrictions.

Modified Atkins Diet (MAD), based on the Atkins diet, the main goal of which was to lose weight by increasing fats and reducing the percentage of carbohydrates in the diet. The GKI in MAD is 1:1 or 2:1. The most important restriction of this diet is the total allowable daily carbohydrate intake. In children during the first month of therapy, the carbohydrate supply is 10g/day and increases in the second and third month to 15 and 20g/day, respectively. In adolescents, the initial carbohydrate intake is 15g/day in the first month, increased to 20 and 25g/day in the second and third month. Because MAD allows for lower dietary restriction compared to CKD, it is often preferred in adolescent and young adult populations [52].

Medium Chain Triglyceride Diet (MCTD) is a variation of KD developed in the 1950s. The main advantage of this diet is that it is more digestible than classic KD, and therefore easier for patients to maintain. MCTD is based mainly on eight and ten-carbon fatty acids, providing more ketone bodies per kcal compared to classic KD, which relies mainly on short-chain fatty acids. Fats provided in MCTD are better absorbed and more efficiently transported to the liver via the portal system. The high ketogenic potential of MCTD, allows for a lower total daily fat supply and a higher proportion of carbohydrates and proteins in the diet. This fact makes MCTD preferable in the paediatric population due to the possibility of greater menu variety, compared to CKD [53]. The effectiveness of MCTD in seizure control in epileptic patients is comparable to that achieved with CKD, as verified by many studies [55,56,57].

Low Glycaemic Index (LGIT) is one of the newest treatments, a variation of MCTD, first introduced at Massachusetts General Hospital in Boston, USA, in 2002, and is the most liberal of all KD variations, as it allows patients to consume 40–60g of carbohydrates/day. A probable hypothesis explaining the mechanism of action of LGIT in epileptic patients is the stability of blood glucose levels, instead of high concentrations of serum ketone bodies. Studies conducted on epileptic patients treated with LGIT have so far failed to provide conclusive results as to its effectiveness in controlling the condition. The proportion of individual components in the cited diets is shown in Table 2. Knowledge of the effectiveness of the new types of KD is crucial for clinical practice, as it allows for the selection of appropriate treatment for the individual needs of the patient, depending on the type of epilepsy, general condition, age and available financial resources [58].

Table 2. Proportion of fats, proteins and carbohydrates in different variations of KD

Type	Fat (g)	Protein (g)	Carbohydrate (g)	% of total fat calories
CKD	100	17	8	90
MCTD	78	25	50	70
MAD	70	60	10	70
LGIT	60	40	40	45

Abbreviations in text.
Source: based on [53].

Effect of KD on metabolism. The positive effect of KD on patient weight is supported by numerous scientific studies, while there are conflicting reports on its effect on glycaemic control. Some studies suggest that KD can induce hepatic insulin resistance, although KD-fed animals presented relatively lower plasma glucose levels. Murakami et al. quote that human studies show positive effects of KD on glycaemic control, weight and lipid profile in obese patients, compared to patients on non-fat diets. There are also reports of KD effects on changes in adipose tissue immune cells [59]. Luong et al. indicate the beneficial effect of high levels of ketone bodies on the cardiovascular system. The reasons for this effect are attributed to improved cardiac energetics and reduced oxygen consumption by the heart muscle. KD has the potential to both treat and prevent cardiovascular disease. In addition, the authors mention that the diet also has side-effects, among which they cite hyperlipidaemia, and an increase in plasma triglyceride and LDL-C levels as the most important. The difficulty for patients to maintain the diet, as well as the lack of knowledge of its long-term effects, do not allow the large-scale use of KD in cardiovascular disease [60]. A 2020 meta-analysis examining the effect of KD on metabolic parameters in overweight, obese and type two diabetic or healthy patients confirms the positive effect of KD on glycaemic control in diabetic patients compared to the results obtained in patients on low-fat diets. The results were compared in terms of glycated haemoglobin levels and homeostasis model assessment index. Differences between patients without diabetes were comparable. In addition, KD contributed to significant weight reduction, regardless of whether or not the subjects were diabetic, and reduced triglycerides and increased HDL-C levels in diabetic patients. The effects described in the article may contribute to improved health status and mortality rates in the patient groups studied [61].

Effect of KD on cancer cells and gene expression. Cancer cells require increased energy due to their increased rate of division. In non-cancerous cells, carbohydrates enter the glycolysis pathway to produce pyruvate, which is then incorporated into the Krebs cycle. In contrast, cancer cells generate most of their energy through glycolysis. This phenomenon is known as the Warburg effect, explained by the dysfunction of glycolytic and ketolytic enzymes in the mitochondria of cancer cells. Studies supporting the thesis of the anti-cancer effect of the ketogenic diet explain its possible mechanism of action by mitochondrial dysfunction and reduced expression of ketolytic enzymes in cancer cells. When blood glucose levels drop during the ketogenic diet, non-cancerous cells begin to use ketone bodies as an energy source, while cancer cells lose a potentially major energy source.

Studies on the effects of the KD in cancer suggest that it may be effective as an adjunct to standard anti-cancer therapy, but according to current knowledge it is unlikely to be a primary therapeutic option [62]. The effect of KD on gene expression occurs through histone acetylation. This process promotes transcription activation, and is modulated through two main enzymes: histone deacetylase (HDAC) and histone acetyltransferase (HAT). The positive charge of histone proteins is neutralized by the acetyl groups attached by HAT, which reduces the strength of histones' interactions with DNA and allows RNA polymerase to attach to the

promoter region of the gene. HDAC reverses this process by disconnecting acetyl groups from histone proteins, leading to transcription repression. At the very beginning, oxaloacetate is diverted into the gluconeogenesis pathway. However, when the level of ketone bodies increases, hepatic gluconeogenesis is suppressed, allowing oxaloacetate to react with acetyl-CoA to produce citrate. After transport to the cytoplasm, citrate is converted back to acetyl-CoA, which serves as a donor of acetyl groups for HAT in the cell nucleus. Excess acetyl-CoA is also involved in HAT-independent protein acetylation. This process indicates a major role for KD in regulating gene expression [59].

Anti-oxidant activity and interaction of ketone bodies with G protein-coupled receptors. Ketone bodies, in addition to their role as energy substrates for the brain, heart and skeletal muscles in malnutrition, also have an important role in regulating the body's inflammatory response. Beta-Hydroxybutyrate (BHB) has been shown to have protective properties against nerve cells. In cells treated with BHB, there was a decrease in the Nicotinamide adenine dinudeaotid (phosphate) NADP+/NADPH ratio in the cytoplasm and an increase in the concentrations of the reduced form of glutathione. In addition, neurons treated with ketone bodies showed reduced concentrations of semiquinone. In cells subjected to pro-inflammatory LPS stimulation, BHB suppressed the inflammatory response by inhibiting transcription factors that regulate gene expression for pro-inflammatory iNOS, COX-2, INF-alpha, IL-1beta and IL-6.

The anti-oxidant properties of ketone bodies have positive effects on the course of diseases such as spinal cord injury, Alzheimer's disease, stroke/heart attack and hypertension [62]. Many key metabolites, such as short-chain fatty acids (SCFAs) and bile acids, bind to G protein-coupled receptors (GPCRs) affecting intercellular relay pathways and thereby regulating numerous biological processes. There is growing scientific evidence that ketone bodies are themselves signalling molecules. In addition, there are studies indicating that certain GPCRs, such as GPR41, GPR43 and GPR109A, also exhibit the ability to bind ketone bodies. This is another example of how broadly ketone bodies influence physiological processes [59].

Adverse effects of KD. KD therapy is not free of side-effects. Sampaio L. et al. present a study of 51 children of whom about 47% used KD for one year. 43% achieved >90% seizure control, 39% achieved control estimated at 50–90%, and only 17% did not respond well to therapy, achieving less than 50% seizure control. Side-effects observed among patients included lethargy, dehydration, acidosis, mood changes, increased susceptibility to infection, constipation and vomiting [51]. De Lima P. et al. examined the effects of a classical ketogenic diet on populations of children and adolescents with drug-resistant epilepsy. The authors cite hypocalcaemia, hyperuricemia, nephrolithiasis, dyslipidaemia, metabolic acidosis, and gastroenterological disorders, such as diarrhea, constipation, and vomiting as the main side- effects of this therapy. The main abnormalities in laboratory parameters included changes in the lipid profile: increases in LDL cholesterol (LDL-C) and triacylglycerols (TG) [63]. As mentioned above, KD therapy may be associated with hypocalcaemia in patients receiving this therapy. This appears to result in inadequate bone mineralization with prolonged KD use. There is a divergence in studies examining this issue: Bergqvist et al. described a decrease in lumbar vertebral mineral content (by 0.6 and 0.16 standard deviations per year, respectively) in patients on KD [87].

The International Ketogenic Diet Study Group recommended periodic measurement of the bone status of such patients by dual energy X-ray absorptiometry (DEXA). In contrast. more recent reports do not describe such abnormalities: a cohort study of GLUT-1 deficient patients on KD for five years and a study by Svedlund et al. on patients on MAD, showed complete safety of the diet on bone mineralization with vitamin D supplementation. More studies in this area are needed to produce clear recommendations for supplementation and differences in therapy in patients with bone disorders [87,88].

It is also worth mentioning the effect of KD on a child's growth and development. An inadequate diet, without the required caloric supply, an underlying disease (in this case epilepsy) and the phenomenon of ketosis can have a negative impact on growth and development. Studies by Williams et al, Vining et al. and Spulber et al. noted a decrease in children's growth in relation to percentile grids during KD administration. The decrease was greater the longer the duration of KD therapy. However, in these studies, patients followed diets with 75% of the required caloric supply for their age in order to enter ketosis and observe therapeutic effects more rapidly [87]. In contrast, more recent studies without caloric restriction in KD, with appropriately managed diets (as much as 90% of energy from fat and 10% from protein), and with adequate supplementation (multivitamin, calcium citrate, potassium citrate) showed minor adverse effects. From a cohort of 151 patients, only three showed slight growth abnormalities (one standard deviation) [87,89]. Thus, the effect of KD on the availability of nutrients required for growth and development alone should not be negative with properly administered therapy. However, further research is necessary on the possible effects of ketone bodies on endocrine pathways important in growth regulation [90].

KD in epilepsy treatment. During KD therapy, the body begins to derive energy primarily from fatty acid oxidation in the mitochondria, resulting in the production of large amounts of acetyl-CoA. The accumulation of acetyl-CoA leads to increased synthesis (mainly hepatic) of two major ketone bodies: BHB and acetoacetate, and the ketone bodies can then be used as an alternative energy source for the brain instead of glucose. This is made possible by special transporters in the blood-brain barrier and mitochondrial enzymes in brain cells. It has been proven that KD stimulates the synthesis of the afore-mentioned proteins and promotes the use of ketone bodies as the main source of energy for the brain. Upon entering the brain, ketone bodies are converted into acetyl-CoA to be directed to the Krebs cycle in the mitochondria, leading to the production of ATP (Adenosine triphosphate) (Fig. 1). KD thus contributes to a significant increase in energy production in the brain. Sustained KD therapy upregulates many genes that modulate brain metabolism, increases mitochondrial biogenesis and density, and leads to an increase in brain energy reserves such as phosphocreatine. Increased energy production allows neurons to better cope with metabolic stress potentially contributing to a decrease in the frequency of epileptic seizures, and an increase in epileptic threshold [53].

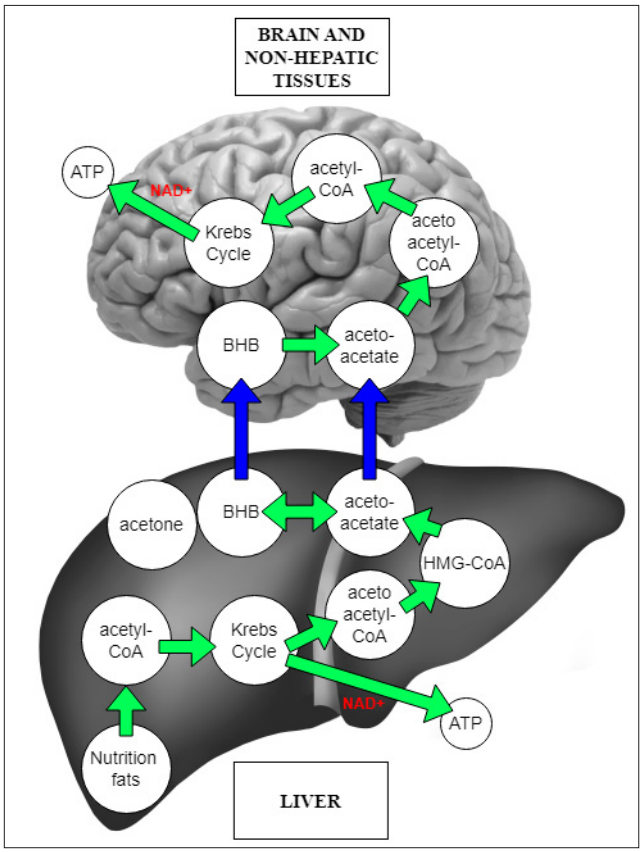

Figure 1. Metabolism of ketone bodies in liver and other tissues

KD versus potassium channels. ATP-gated potassium channels are widespread in the human body, and are also found in the Central Nervous System (CNS). The main factor influencing their activity is the ATP/ADP ratio and ATP-driven Na+ pumps in the membrane of CNS neurons. When KD is used, K_{ATP} channels are opened and the membrane of neurons is hyperpolarized due to reduced use of glycolysis in ATP production. This leads to decreased electrical excitability and increased seizure threshold [53]. Two-pore domain K channels (K2P), or potassium leak channels, are the second type of potassium channels present in the membrane of CNS nerve cells. Functionally, these channels maintain the membrane of neurons in a hyperpolarized state, necessary for maintaining the resting potential through a constant flow of potassium ions. For this reason, K2Ps are directly responsible for the frequency of action potentials generated in the CNS. It has been suggested that ketone bodies and certain fatty acids are factors modulating K2P action. For this reason, it is speculated that K2P is another potential mechanism that may explain the effects of KD on epileptic patients [53].

KD versus neurotransmitters. GABA (Gamma-amonobutyric acid), a glutamate receptor, is the main inhibitory neurotransmitter of the brain reducing neuronal excitability, and for this reason has a crucial role in controlling the epileptic activity of CNS neurons [53]. KD can also exert anti-convulsant effects by increasing GABA synthesis and decreasing glutamate production. Increased levels of GABA have been reported in the cerebrospinal fluid of patients on KD. A decrease in aspartate levels has also been observed due to the utilization of oxaloacetate in the Krebs cycle, which translates into inhibition of GAD (glutamate decarboxylase) and increased conversion of glutamate to glutamine in astrocytes [54]. Acetoacetate modulates $GABA_A$ receptors and inhibits glutamate transporter activity, thereby reducing glutamate release and excitation frequency in the rat hippocampus. In addition, it has been suggested that ketone bodies inhibit vesicular glutamate transporters (VGLUTs), reducing glutamate release during synaptic transmission [54]. Agmatine (4-aminobutyl-guanidine) is a metabolite of L-arginine, widely distributed in the CNS, mainly in the hippocampus, and is considered one of the inhibitory neurotransmitters. It exerts a potential anti-convulsant effect through inhibition of excitatory receptors, such as NMDA, epinephrine and histamine receptors. A study cited in the article, shows an increase in agmatine levels in the hippocampi of KD-treated rats [53]. It has also been noted that it may act synergistically with the AEDs: valproic acid, phenobarbital and vigabatrin [54]. This is another mechanism potentially explaining the effect of KD on epileptic patients. Other neurotransmitters with potential effects on epileptic seizure control in KD patients include norepinephrine, serotonin, dopamine, galanin and neuropeptide Y. The exact effect of KD on the afore-mentioned neurotransmitters has not been fully elucidated to date. There is a need for further research to unequivocally prove their role in the anticonvulsant mechanism of KD [53].

Another cited study confirms that norepinephrine, as well as the orexigenic neuropeptide galanin, are among the two classes of substances contributing to the anti-convulsant effect of KD. However, in children with drug-resistant epilepsy, KD does not significantly alter the concentrations of these compounds, but it does significantly affect the levels of dopamine and serotonin metabolites in the cerebrospinal fluid. In addition, an increase in GABA and agmatine levels was observed with no change in glutamate levels within the hippocampus of rats subjected to KD for 15 days compared to control rats. These data support the hypothesis that KD influences the generation of epileptic potentials by modifying various neural transmission pathways, favouring inhibitory neurotransmitters over the excitatory neurotransmitters.

Another potential mechanism of action of KD is the kynurenine pathway. Kynurenic acid, a metabolite of this pathway, is involved in the pathogenesis of seizures. Ketone bodies produced in increased amounts during KD, reduce glutamate levels, which contributes to inhibition of the kynurenine pathway and a decrease in kynurenic acid levels. Stimulation of mitochondrial metabolism during KD, contributes to up-regulation of uncoupling proteins. The properties of these enzymes, allow the degradation of reactive oxygen species (ROS) that promote epileptic seizures, potentially reducing the frequency of epileptic discharges. In addition, increased levels of glutathione were also observed in KD subjects, which, by degrading ROS, protects mitochondrial DNA from oxidative damage. Reduced glycolysis in brain cells during KD, can induce the production of ATP-gated potassium channels (K channels sensitive to ATP opening), leading to hyperpolarization of the neuron's cell membrane, increasing the epileptic threshold. Other factors affecting the reduction of seizure frequency in KD patients include polyunsaturated fatty acids, which also affect the synthesis of neuronal uncoupling proteins, regulation of gene expression important for brain metabolism, and induction of mitochondrial biogenesis [64].

Although some studies have suggested a direct relationship between plasma concentrations of BHB and the frequency of epileptic seizures, a consensus on this issue has not yet been reached. Pre-clinical studies indicate the anti-convulsant properties of acetone in pentylenetetrazole- and 4-aminopyridine-induced seizures. Furthermore, BHB shows anti-convulsant properties in Kcna1-null mutant mice, which recapitulates seizures in human TLE. In addition, the article shows positive effects of acetoacetate on thujone-induced seizures in rabbits and on sensorium-evoked seizures in Frings audiogenic seizure-susceptible mice.

In conclusion, *in vitro* studies in rodents have shown that the anti-convulsant effect of BHB and acetoacetate is dependent on the site of application in the CNS. Authors also cite GABA and glutamate as one possible mechanism through which KD exerts its positive effects on epileptic patients. The paper supports the thesis that KD increases GABA levels; however, the effect on glutamate concentrations remains controversial. Also described is the effect of KD on the expression of KCC2 channels in rats on KD for longer than three months. These channels inherently enhance GABA transmission, which may contribute to the anti-convulsant effect. Alternatively, KD may reduce the frequency of epileptic discharges by modifying acetoacetate-mediated presynaptic glutamate output, which is supported by results from rat studies. Other potential mechanisms are found in modification of mitochondrial metabolism and ROS production, increased synthesis and ejection of inhibitory adenosine, effects on K_{ATP} channels and $GABA_B$ inhibitory receptors. Also of interest seems to be the effect of KD on the gut microbiota. Recent reports suggest an important role for the gut-brain axis in the pathogenesis of epileptic seizures in drug-resistant patients. Nevertheless, this hypothesis requires further research [59].

Therapy effectiveness. A study was conducted on 150 children between the ages of one and 16, with an average monthly seizure count of 410 before starting KD. One year after starting the study, 27% of the children showed >90% reduction in seizure frequency, 7% achieved complete seizure freedom, and 50% showed >50% reduction in seizure frequency. The first three months proved crucial to the success of the therapy. Children who achieved >50% seizure reduction during this period showed systematic improvement as the study continued, while those who did not reach the 50% threshold were unlikely to improve. The article also cites a study on an adult population, a meta-analysis, conducted in 2011, consisting of 270 patients, among whom 168 received CKD, 87 received MAD, and 15 received a combination of MCT and CKD. The efficacy rate in the group of adults with drug-resistant epilepsy ranged from 13–70%. The overall efficacy rate of CKD was estimated at 42%, noting the high variability between the studies analyzed [51].

Another study conducted between 1 April 2016 – 20 August 2017, included 170 children aged between one and 15 who had four or more seizures per month, had established drug-resistant epilepsy (no response to two or more drug treatment regimens), and had not previously received CKD, MAD or LGIT therapy. The subjects were randomly assigned to receive CKD, MAD or LGIT treatment with maintenance of the pharmacological treatment used to date. Seizure frequency reduction results were compared between the MAD and CKD treatment groups, and the LGIT and CKD treatment groups. The aim of the study was to compare the effectiveness of the three afore-mentioned diets in reducing seizures and side- effects. Among MAD and CKD, no better treatment option emerged, according to the criteria established by the authors. LGIT, on the other hand, showed a better balance in reducing seizure frequency and side-effects, compared to MAD and CKD [65].

In a review article based on COCHRANE, EMBASE, MEDLINE, and other highly- qualified databases, randomized controlled trials from January 2011 – January 2020 were selected for analysis. The meta-analysis found that the KD-treated group of patients was 5.6 times more likely to achieve a 50% reduction in seizure frequency after three months of therapy, compared to a control group not treated with KD [66]. In an analysis of the literature on paediatric epileptic patients, studies containing a minimum of one infant under two years of age treated with KD for >= 1 month were selected. In this meta-analysis, the authors estimate that 59% of patients achieved >50% seizure reduction, 33% achieved full seizure freedom. The retention rate was 84% and 27% at three and 24 months of the study, respectively. The most common side-effects reported were dyslipidaemia (12%), vomiting (6%), constipation (4%), gastroesophageal reflux (4%) and diarrhea (4%) [66]. Another study looked at patients with Dravet syndrome.

An analysis of PubMed, Embase, Wanfang and CNKI databases was conducted to evaluate the effectiveness of KD in reducing seizures and retention rates. Seven studies, involving a total of 167 patients, met the admission criteria of which four were retrospective and three were prospective. The meta-analysis revealed a seizure reduction of >=50% in 63%, 60% and 47% of subjects at months three, six and 12, respectively. The retention rate was 78% at month six and 49% at month 12 [68]. KD is also proving to be an effective therapeutic tool in the treatment of drug-resistant epilepsies caused by structural changes in the CNS. A retrospective analysis of 23 pediatric patients was performed in 2022, with the data covering the period from May 2014 – December 2020. Patients were divided into thee groups: group 1 – patients with neonatal brain injury, group 2 – patients with intracranial infection, group 3 – patients with cortical malformations Seizure reduction of >50% was most often achieved by patients in group 1. Further analysis also showed that children in group 1 with a history of hypoxaemic encephalopathy achieved seizure reduction of >50% most often (100%, 6/6) [69]. A 2020 prospective study analyzed the effect of KD on the first 100 adult epilepsy patients treated at the National Hospital for Neurology and Neurosurgery in London. The study lasted one year, with patients undergoing dietary control twice a week. Of these, 42 were started on KD therapy. The subjects had previously taken an average of four anti-epileptic drugs. The retention rate was 60% at month three, 43% at month six and 29% at month 12. 60% of patients reported improvement in seizure frequency, 38% achieved >50% reduction in seizure frequency, and 13% reported a period of complete seizure freedom. Deterioration of the disease course, on the other hand, was reported by 30% of patients at any point during the experiment [70].

Roehl et al. carried out a retrospective study that analyzed changes in seizure frequency and severity, quality of life and sid- effects in adult patients >17 years of age with drug-resistant epilepsy, after three months of KD therapy. 60% of subjects reported a reduction in seizure frequency >= 50%, 76% reported an improvement in seizure severity, and 87%

reported an improvement in quality of life [71]. Husari K.S. et al. compared the effectiveness of KD in adult epileptic patient populations. A positive response to therapy (defined as a reduction in seizure frequency >=50%) was achieved by 17% – 60% of patients, depending on the study [72]. Studies of KD in the treatment of drug-resistant epilepsy in adults have so far provided solid evidence of the efficacy of the discussed diet in the treatment of this condition [49]. If effective and tolerated, the KD therapy usually lasts for two years. This is analogous to the common practice of terminating pharmacotherapy after that period in children who have achieved seizure control. However, KD therapy can be continued significantly longer, for instance in patients with GLUT-1 (glucose transporter) deficiency syndrome [86].

Although there are reports that in paediatric patients that it is possible to maintain seizure control after returning to a normal diet [85], there is a lack of studies in the adult population on the effect of KD termination and epileptic seizure control [86]. In a randomized trial, a group of paediatric patients with West syndrome who achieved seizure control with KD were divided into two groups. In the first group, therapy was discontinued after eight months, and in the second – after two years. It was shown that there was no difference in seizure recurrence between the two groups. Because of the possible side-effects of the diet, such as growth disorders, the authors recommend faster discontinuation of KD in the paediatric patient group [85]. The return from KD to a normal diet should be gradual, over weeks or months; the longer the child has been treated with KD, the longer this period should become. During KD withdrawal, it is recommended to systematically reduce the GKI by 0.25, 0.5, or 1.0 every few days. However, in the case of a poor response to KD if seizure control has not been achieved, a return to a normal diet can be carried out over several weeks. During this process, it is advisable to check the level of ketone bodies. If they are no longer present in the blood or urine, a full transition to a normal diet can be performed [85]. Similar recommendations for discontinuing KD apply to the adult population. KD should be discontinued, especially slowly in patients who have been on therapy for a long time, and in those who have achieved spectacular seizure control with its help. Adults may be reluctant to stop therapy, especially if the response has been satisfactory. If seizure frequency has increased during discontinuation, the medical team should consider a slower GKI reduction or KD continuation [86].

KD in other neurological diseases. The implementation of KD into therapy or modification of the current diet may also be helpful in the treatment of other neurological diseases. The therapeutic activity of reduced glucose supply and higher fat supply has been observed in neurodegenerative diseases (such as Parkinson's or Alzheimer's disease) as well as in depression or migraine. Degeneration of substantia nigra which disrupts dopaminergic transmission, is responsible for the development of symptoms in Parkinson's disease, so L-DOPA is used in treatment to replenish the neurotransmitter [73]. KD through reduced protein supply, significantly improves the bioavailability of L-DOPA (1–3, 4 dihydroxyphenylaline), an amino acid that can cross the blood-brain barrier [74]. In addition, BHB exhibits a protective effect on dopaminergic neurons. It is due to increased efficiency of the mitochondrial electron transport chain, increased ATP production and reduction of ROS (reactive oxygen species) [75]. Alzheimer's disease, currently incurable, develops on the basis of numerous mechanisms of neurodegeneration. One of the most important is the deposition of pathological β-amyloid protein plaques in the grey matter of the brain and in the cerebral vessels. This leads to structural changes and micro-haemorrhages that result in progressive dementia symptoms [76].

The diet, not so much the KD as the consumption of Mediterranean products (e.g. olive oil, walnuts), is helpful in therapy. Oleuropein contained in olive oil, has been shown to have a neuroprotective effect by reducing the deposition of β-amyloid aggregates and improving synaptic activity, while anti-oxidants, such as n-3 α-linolenic acid, have an anti-inflammatory effect [77].

Migraine, as a disorder affecting up to 20% of patients in some regions, manifests mainly as severe headaches and disturbances of consciousness. It has been found to develop on the basis of channelopathy, vasomotor disorders and impaired brainstem stimulation [78, 79]. KD, particularly the resulting ketosis, reduces hypoglycaemia, increases inhibitory neurotransmitters (GABA), and exhibits ant-ioxidant effects. All mechanisms collectively contribute to a reduction in the frequency and severity of migraine attacks [80]. The pathophysiology of depression is based on disturbances in neurotransmitter systems like dopamine, norepinephrine and serotonin. Serotonin is formed from tryptophan, an excellent source of which are eggs or pumpkin seeds, products used regularly in KD [81]. In addition, BHB, by inhibiting the HDAC (histone deacetylase) enzyme in a previously-described mechanism, increases the secretion of brain-derived neurotrophic factor (BDNF) acting neuroprotectively which translates into improved mood [82, 83].

KD is also the subject of numerous studies in the treatment of psychiatric diseases, such as anorexia nervosa, autism spectrum disorders, bipolar disorder, narcolepsy and schizophrenia. In all of these, KD can reduce the severity of clinical symptoms [84].

CONCLUSIONS

1. Epilepsy is a severe disease of the CNS, it can lead to serious complications and its causes are extremely broad.
2. Classical therapy is based on pharmacology, but in the case of drug-resistant epilepsy, surgery or alternative methods, such as implementing KD, should be considered.
3. KD is based on a low carbohydrate supply and high fat supply, which promotes the use of ketone bodies and positively affects metabolism in many tissues.
4. KD in epilepsy therapy increases energy which allows neurons to manage metabolic stress more effectively and prevent seizures.
5. The effect of KD on ion channels and multiple neurotransmitters is also a mechanism in epilepsy therapy.
6. KD is a very effective method but should be administered with caution and adequate supplementation of microelements due to possible side-effects.
7. KD is also applicable in neurological and psychiatric disorders.

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