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THE ROLE OF THE KETOGENIC DIET IN THE TREATMENT OF EPILEPSY IN CHILDREN AND ADOLESCENTS - A REVIEW OF THE LITERATURE

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ABSTRACT

Introduction: Epilepsy affects around 50 million people worldwide and is marked by recurrent seizures due to abnormal brain activity. While anticonvulsant medication (ASM) is the standard treatment, about 30% of patients develop drug-resistant epilepsy (DRE), requiring alternative therapies. One such approach is the ketogenic diet (KD), a high-fat, low-carbohydrate regimen that mimics fasting metabolism. Recent research has explored its mechanisms and efficacy in epilepsy management.

Aim of the Study: This study evaluates the effectiveness and mechanisms of KD in treating drug-resistant epilepsy in children and adolescents.

Materials and Methods: A PubMed analysis was conducted using keywords: ketogenic diet, epilepsy, drug-resistant epilepsy, seizure control, metabolic therapy.

Basic Results: Studies confirm KD's ability to reduce seizure frequency and severity in children with DRE. Over 50% of patients on KD show significant seizure reduction, with some achieving complete freedom. Though side effects like gastrointestinal discomfort and dyslipidemia occur, they are generally manageable. EEG studies suggest KD improves epileptiform discharges, offering broader neurological benefits.

Conclusion: KD is a proven, effective therapy for DRE in children, working through increased GABAergic inhibition, metabolic shifts, and neuroprotection. Clinical trials show its ability to reduce seizures, enhance cognition, and improve EEG patterns. While adherence can be difficult, modified versions like MAD offer flexibility. KD's long-term safety is acceptable, with manageable side effects. Future research should explore its potential as a primary therapy, reducing reliance on ASMs.

Keywords: ketogenic diet, epilepsy, drug-resistant epilepsy, seizure control, metabolic therapy

INTRODUCTION

Epilepsy is a neurological condition characterized by abnormal neuronal activity in the brain that manifests as epileptic seizures. It is one of the most common diseases of the nervous system, affecting some 50 million people worldwide, according to the first global report on it. Most children with epilepsy use anticonvulsant medication (ASM) as their primary treatment to control seizures. However, about 30% are diagnosed with drug-resistant epilepsy (DRE), which occurs when two appropriately selected ASM therapies are unable to effectively reduce seizures. In such situations, alternative treatments such as surgery, neurostimulation devices or the ketogenic diet (KD) are considered.[5] Spontaneous and recurrent epileptic seizures (SRS), a characteristic symptom of epilepsy, are associated with increased excitability of neurons and their excessive synchronization. These mechanisms can result from both genetic factors and brain injury and are modified by a variety of environmental factors. Regardless of the cause, these processes require significant amounts of energy - both to prevent the development of seizures (ictogenesis) and to power prolonged seizure activity, as well as regeneration and repair afterwards. Indeed, adequate levels of ATP, the body's basic energy unit produced mainly in the mitochondria, are crucial for restoring the membrane potentials that enable epileptiform activity. Therefore, treatments based on metabolic support, such as the ketogenic diet, which provides the brain with an alternative energy source in the form of ketone bodies, are particularly effective in preventing seizures and promoting recovery after they occur.[1]

The ketogenic diet (KD) is a way of eating that is based on eating high-fat, low-carbohydrate meals. The diet's action is based on using fat, instead of glucose, as the main source of energy through the production of ketone bodies.[2] The ketogenic diet mimics the fasting state while providing the body with enough calories to promote growth and development. The classic form of KD (CKD) is based on a 4:1 macronutrient ratio (four parts fat to one part protein and carbohydrates combined), changing the main source of energy from carbohydrates to fat. The metabolism of fatty acids in the liver produces ketone bodies, such as acetoacetate, acetone and β-hydroxybutyrate, which are transported to organs, including the brain, and used for energy production in the mitochondria. On a ketogenic diet, ketone bodies become the main source of fuel for the brain instead of glucose. Elevated levels of ketones in urine or serum serve as an indicator of adherence to the diet, although their levels are not always associated with a reduction in epileptic seizures. Less restrictive variants, such as the modified Atkins diet (MAD), low glycemic index therapy (LGIT), or diets with medium-chain triglycerides (MCTs), have been developed to increase dietary acceptability. Less stringent macronutrient ratios, such as 3:1, 2:1 or 1:1, are often chosen depending on the patient's age, tolerance, level of ketosis and protein needs.[3]

Current recommendations for the use of the ketogenic diet in the treatment of epilepsy are detailed in guidelines developed by the International Study Group on the Ketogenic Diet in 2009 and 2018. These documents provide practical guidance on patient eligibility, preparation for starting the KD, choosing the right type of diet, its introduction, supplementation, monitoring the effects of therapy, dealing with side effects, and rules for quitting the diet. [4.]

CONTENT OF THE REVIEW

PROBABLE MECHANISMS OF THE KETOGENIC DIET IN THE TREATMENT OF EPILEPSY

Over the past decade, significant advancements have been made in understanding the mechanisms underlying the ketogenic diet (KD), yet its exact clinical effectiveness in treating seizure disorders remains incompletely understood. It is likely that multiple interconnected mechanisms work simultaneously to produce both anti-seizure and neuroprotective effects. The following sections discuss key proposed mechanisms of action for KDs. [6]

Studies have shown that KD can increase gamma-aminobutyric acid (GABA), adenosine, and norepinephrine levels while decreasing glutamate levels. In astrocytes, glutamate is transformed into glutamine, which is transported to neurons and converted back into glutamate. This glutamate can then be converted into either GABA or aspartate, with oxaloacetate playing a crucial role in the latter process. [6,7] However, during KD, ketone body metabolism increases oxaloacetate production, which is redirected into the tricarboxylic acid (TCA) cycle for energy, reducing its availability for aspartate synthesis and favoring GABA production. Additionally, ketone bodies like beta-hydroxybutyrate and acetoacetate inhibit chloride ions that regulate vesicular glutamate transporters, leading to reduced glutamate release. KD also suppresses adenosine kinase activity, enhancing extracellular adenosine levels and stimulating adenosine A1 receptors, which contribute to inhibitory effects. Increased extracellular norepinephrine levels have also been documented. [6,8]

Another mechanism is based on reduction of neuronal firing rates by activating ATP-sensitive potassium channels and GABAB receptors. Studies have shown that slower firing of the neurons is caused by

opening of the potassium channels, which proccess is induced by the metabolism of keton bodies. [6,9] Acetoacetate has also been found to inhibit voltage- dependent calcium channels, lowering excitatory postsynaptic currents. Medium-chain triglyceride (MCT) KDs elevate plasma levels of decanoic acid, which acts as a selective non- competitive antagonist of AMPA receptors, further contributing to seizure control.

Ketogenic diet can also reduce glycolysis and increase fatty acid metabolism, which lowers neuronal excitability. Polyunsaturated fatty acids (PUFAs) associated with KD influence voltage-gated potassium channel sensitivity, promoting channel opening and reducing cellular excitation. KD also enhances the expression of PPARγ, a transcription factor regulating anti- inflammatory and antioxidant pathways, which reduces pro-inflammatory cytokines like interleukin-1β, known to contribute to seizure generation. [6]

The ketogenic diet may play a significant role in managing epilepsy by exerting neuroprotective effects and reducing oxidative stress. Research highlights that the epileptogenic state involves complex molecular pathways where oxidative stress and mitochondrial dysfunction are key contributors to neuronal cell death. This cell death may occur through programmed mechanisms, such as apoptosis, or passive processes, such as necrosis. Therefore, considerable attention has been given to the ketogenic diet's influence on mitochondrial biogenesis in neurons, emphasizing the mitochondria's central role in preventing cell death and regulating apoptosis. Mitochondria, essential intracellular organelles, are primarily responsible for producing cellular energy in the form of adenosine triphosphate (ATP). ATP is synthesized through oxidative phosphorylation in the mitochondrial respiratory chain, which consists of five multienzyme complexes (I-V). Dysfunction in complex I, frequently associated with neurological disorders, can lead to reduced ATP production. During prolonged seizures, temporary decreases in ATP levels can worsen neuronal damage and contribute to cell death. A study by Bought et al. demonstrated that mice fed a ketogenic diet for at least three weeks showed a 46% increase in mitochondrial biogenesis in the hippocampus compared to control animals. The ketogenic diet has also shown significant antioxidant benefits, particularly by enhancing the function of glutathione (GSH), a key molecule in cellular peroxide detoxification. In juvenile rats maintained on the diet for three weeks, increased levels of mitochondrial-reduced GSH and an elevated GSH-to- oxidized glutathione (GSSG) ratio were observed. These results indicate that the ketogenic diet improves hippocampal redox balance and protects mitochondrial DNA from oxidative stress. Since seizures often deplete antioxidants and heighten oxidative stress, the ketogenic diet's ability to counteract these effects highlights its neuroprotective potential in epilepsy management. [10]

EARLY STUDIES ON KETOGENIC DIET IN TREATMENT OF EPILEPSY

The first reports on the use of the ketogenic diet in the treatment of idiopathic epilepsy date back to 1931. That year, The Canadian Medical Association Journal published information about a study presented at a meeting of the American Medical Association. This study focused on the application of the ketogenic diet in patients at the Mayo Clinic. Between 1921 and 1930, the ketogenic diet was implemented in 272 children. After excluding those unable to cooperate and continue participation in the study, 171 individuals remained. Of these, 141 children remained on the KD for more than one year, while 30 followed it for less than a year. Among the first group of 141 children, 43 remained seizure-free for a period ranging from 1 to 7 years. In 32 cases, although seizures did not cease entirely, significant improvements were observed in terms of reduced frequency and severity of episodes. In the remaining 66 patients, the treatment showed no effects. As for the group of 30 children who adhered to the diet for less than a year, the following outcomes were noted: 11 children experienced no seizures, 13 showed partial improvement, and in 6 cases, the treatment was unsuccessful. It is important to consider that at the time of this study, many of the medications available today were not yet in use. Nevertheless, these findings underscore the fact that the use of the ketogenic diet in the treatment of epilepsy dates back over a century. [11]

One of the first studies about using KD in epilepsy treatment was conducted between January 1st, 1994, and December 30th, 1995 and the results were published in 1998. In this study 51 children with drug-resistant epilepsy were hospitalized and a 4:1 ketogenic diet was initiated and maintained. 88% of children who started the diet were still following it after three months, 69% after six months, and 47% after a year. After three months, over half (54%) experienced a reduction in seizure frequency of more than 50%. At six months, 55% of the 51 participants who began the diet saw at least a 50% reduction in seizures compared to baseline, and after one year, 40% maintained this level of improvement. Additionally, five participants (10%) were completely seizure-free after one year. [12] In the same year (1998) another study was published, conducted by a group from John Hopkins. A total of 150 children, aged 1 to 16 years, were included in this study. Nearly all participants continued to experience more than two seizures per week despite receiving appropriate treatment with at least two anticonvulsant drugs. These children were prospectively enrolled, started on the ketogenic diet, and monitored for at least one year. At the three-month mark after starting the diet, 83% of participants continued with it, and 34% experienced a reduction in seizures of over 90%. After six months, 71% were still following the

diet, with 32% achieving a greater than 90% decrease in seizures. By one year, 55% of participants remained on the diet, and 27% had reduced their seizures by more than 90%. The majority of those who discontinued the diet did so because it was either not effective enough or too restrictive, while 7% stopped due to illness. [13]

RANDOMISED CONTROLLED TRIALS ON POTENTIAL USE OF KETOGENIC DIET IN TREATMENT OF EPILEPSY

Over the years, numerous randomized controlled trials have been conducted. One of the earliest of these was carried out in 2008 by Neal et al. A total of 145 children, aged 2 to 16 years, who experienced daily seizures (or more than seven per week), had not responded to at least two antiepileptic drugs, and had no prior exposure to the ketogenic diet, were included in this study. The trial's enrollment period spanned from December 2001 to July 2006, with children recruited from two hospital centers and a residential facility specializing in epilepsy care. Participants were randomly assigned to either start the ketogenic diet immediately or delay initiation by three months (control group), with no other changes to their treatment plans. The study was not blinded, as both families and researchers were aware of group assignments. Early withdrawals were documented, and seizure frequency was measured after three months to compare the dietary intervention with the control group. The primary goal was to evaluate seizure reduction, with data analyzed on an intention-to-treat basis. Out of 145 participants, 73 were assigned to the ketogenic diet and 72 to the control group. Data analysis included 103 children—54 from the diet group and 49 controls. The remaining participants either did not receive their intervention, failed to provide sufficient data, or withdrew from the study (including six who stopped due to intolerance). After three months, the diet group showed a significant reduction in seizure frequency compared to the controls. Among the diet group, 28 children (38%) achieved a seizure reduction of more than 50%, compared with four children (6%) in the control group. Additionally, five children (7%) in the diet group experienced a seizure reduction of over 90%, while no child in the control group achieved this. The efficacy of the diet did not differ significantly between children with symptomatic generalized or focal epilepsy syndromes. The most common side effects at the three-month follow-up were constipation, vomiting, fatigue, and hunger. So, in summary, the findings of this study support the use of the ketogenic diet as an effective treatment option for children with drug-resistant epilepsy. [14]

An open, randomized, controlled trial was conducted among children aged 2-12 years with non-surgical DRE. The survey was conducted between October 2019 and May 2021. Participants were recruited from the pediatric neurology and outpatient clinics of Kalawati Saran Children's Hospital in New Delhi. Children were randomly assigned to one of two groups: modified Atkins diet [MAD] (51 children) or levetiracetam (50 children). Seizure frequency was assessed after 12 weeks based on seizure diaries kept by parents. The main objective of the study was to assess the percentage of patients who achieved a >50% reduction in seizures compared to baseline. The incidence of adverse effects was also compared. The study included 101 children, most of whom had generalized mixed-type seizures secondary to structural brain damage, and the most common electroclinical syndrome was Lennox-Gastaut syndrome (46%). After 12 weeks, the percentage of children with >50% seizure reduction was significantly higher in the MAD group than in the levetiracetam group. The mean change in seizure frequency compared to baseline was -47.33 ± 39.57% in the MAD group and -31.15 ± 32.18% in the levetiracetam group ($p = 0.03$). The most common side effects in the MAD group were constipation (41.1%), and in the levetiracetam group were sedation/lethargy (18%), restlessness and irritability (14%). Although MAD has been shown to be more effective in seizure control, compared to levetiracetam, difficulties with dietary compliance can be a challenge, especially in children with recurrent seizures. Nevertheless, the use of MAD has been proven effective, including in low-resource settings. The study found that adding MAD to antiepileptic therapy in children with DRE led to better seizure reduction after 12 weeks, compared to levetiracetam. Both therapies were well tolerated, although side effects were more frequent in the MAD group. MAD is a reasonable alternative to the classic, stricter ketogenic diet and can be used as an initial adjunct to antiepileptic therapy in the treatment of children with non-surgical DRE.[15]

A prospective, randomized study was conducted between 2020 and 2022 to evaluate the efficacy, safety and tolerability of KD and its effects on EEG features among children with drug-resistant epilepsy (DRE). The primary outcome was to evaluate the clinical efficacy of KD (classic KD and MAD) on the occurrence of seizure control, seizure frequency and seizure severity, and to assess the long-term safety of KD with respect to AEs and the effect ofKD on growth and lipid profile. The secondary outcome was to evaluate the effect of KD on EEG features before treatment and 3 and 6 months after KD treatment with the possibility of ASM withdrawal. Patients attending the Pediatric KD outpatient clinic at Menoufia University Hospital were included in the study. Forty patients with DRE were initially included in this prospective study, but only 30 patients successfully completed the study. Six patients (15%) were unable to tolerate KD and were removed from the study (85% tolerance), three additional patients were excluded due to parental incompatibility, and one case died during the study period. The overall reasons for dropping out were mainly diet intolerance, AE (mainly GI-related), weight loss, parental unhappiness and change of mind. Meta-analysis studies confirmed the efficacy of KD and showed a 50% reduction in seizure

frequency (SFR) for both classic KD and MAD. The results showed that 60% of patients in the classic KD group and 46.67% of patients in the MAD group became seizure-free, while the remaining 40% and 53.33%, respectively, had a 50% SFR. KD improved the patients' cognitive and functional status, while reducing the severity and frequency of seizures. Six months after KD, improvements in functional status and cognitive function were noted, with 66.67% of patients in the MAD group and 46.67% of patients in the classic KD group. KD not only showed good clinical efficacy in this study, but also significantly reduced the frequency of interstate epileptiform ejections and improved the background EEG rhythm. This was evident in 22 patients (73.33%) who had EEGs with epileptiform abnormalities (11 in each group) with a reduction in SI > 50% in 8 patients after 1 month, which increased to 14 patients after 3 months and 16 patients after 6 months. The acceptable change in lipid profile with long-term KD (24 months) may be a good indicator of the safety of a high-fat diet on the cardiovascular system in children with DRE. With no reported serious side effects and positive effects on EEG and growth, KD (classic KD and MAD) appears to be an effective and generally well- tolerated therapy for treating children with DRE. It is also recommended that the role of KD as a single line of therapy, either from the beginning or after withdrawal of all other medications once full control is established, is also recommended to be clarified by more studies. [16]

CONCLUSIONS

The ketogenic diet (KD) has shown significant efficacy in reducing seizure frequency and severity in children with drug-resistant epilepsy (DRE). Studies suggest that KD exerts its anticonvulsant effects through multiple mechanisms, including increased GABAergic inhibition, modulation of neurotransmitter levels, activation of ATP-sensitive potassium channels, and neuroprotective effects against oxidative stress. Randomized, controlled trials confirm that KD, including its less restrictive variants such as the modified Atkins diet (MAD), can achieve >50% seizure reduction in a significant percentage of patients. In addition, KD has shown positive effects on cognitive function, EEG patterns and overall functional status. Although adherence to the diet remains a challenge due to dietary restrictions and side effects, its long-term safety profile appears acceptable, with manageable side effects. Future studies should further explore the potential of KD as a primary therapy and investigate its role in replacing or limiting anticonvulsant drugs.

AUTHORS' CONTRIBUTION

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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