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# DRUG-RESISTANT EPILEPSY IN PEDIATRIC PATIENTS: CURRENT EVIDENCE ON THE THERAPEUTIC ROLE OF KETOGENIC DIET

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**ABSTRACT**
**Background:** Epilepsy affects millions worldwide, and approximately one-third of patients develop drug-resistant epilepsy, particularly burdensome in pediatric populations, where comorbid developmental impairments are common and underlying mechanisms remain only partially defined. Emerging evidence indicates that non-pharmacological approaches - most notably modern, better-tolerated ketogenic dietary variants - can reduce seizure burden by including therapeutic ketosis and shifting cerebral energy toward ketone body utilization.
**Materials and methods:** An extensive literature review was conducted using sources retrieved from the PubMed and Google Scholar databases.
**Aim:** The aim of this study was to analyze and synthesize current knowledge and drug-resistant epilepsy in children, as well as to evaluate the role of non-pharmacological interventions, specifically the classical ketogenic diet and its alternative formulations (MAD, LGIT).
**Conclusions:** The classical ketogenic diet (cKD) is effective in children with drug-resistant epilepsy (DRE), but its strict regimen and poor palatability often limit adherence. Alternative approaches, such as the modified Atkins diet (MAD) and low glycemic index treatment (LGIT), are better tolerated and more flexible, though slightly less effective. Further research is needed to clarify underlying mechanisms and optimize dietary therapies for DRE.
**Keywords:** epilepsy, drug-resistant epilepsy, children, ketogenic diet, low glycemic index treatment, modified Atkins diet

## Introduction

Epilepsy is among the most prevalent serious chronic neurological conditions, and it is estimated to affect roughly 68 million individuals worldwide [1]. This disabling disorder occurs in about 0.5% to 1% of the global population and is frequently diagnosed during childhood [2,3]. The term epilepsy refers to a group of brain disorders characterized primarily by recurrent, unpredictable disturbances in normal brain activity, known as epileptic seizures. It does not represent a single disease entity but rather a spectrum of conditions reflecting underlying brain dysfunction arising from various potential causes [4]. In 2010, the International League Against Epilepsy (ILAE) introduced a working definition for drug-resistant epilepsy (DRE). This conceptual framework consists of two hierarchical levels. The first level offers a general structure for classifying the outcome of each therapeutic attempt as either the attainment of seizure freedom or a treatment failure, according to established criteria. The assessment at this initial level serves as the foundation for the second level, which defines drug-resistant epilepsy as a ”Failure of adequate trials of two tolerated and appropriately chosen and used anti seizure medication (ASM) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom” [5,6]. Differences in terminology used to describe refractory epilepsy - such as intractable epilepsy, drug-resistant epilepsy, or pharmacoresistant epilepsy - are largely technical. Under the ILAE definition, the sole factor that should be taken into account is whether the patient has achieved seizure freedom. Conversely, this definition does not incorporate seizure type, seizure frequency, or the presence of additional epilepsy-related complications. Persistent confusion often stems from questions such as how many medications must fail or how seizures should be counted within a specific period [7,8].

The onset of epilepsy may be linked to numerous contributing factors, including genetic predisposition, malformations, traumatic brain injury, exposure to neurotoxic chemicals, hypoxic, or cerebrovascular accidents [9]. Analyses investigating predictors of drug-resistant epilepsy (DRE) revealed that the emergence of epilepsy during the first year of life represents one of major risk factors. Drug resistance has also been associated with psychomotor delay and intellectual disability, and disturbances in language, attention, and behavior appear to exert an important influence as well. It is essential to emphasize that due to the multifactorial nature of DRE, the resulting phenotype is shaped not only by the independent effects of specific risk factors but also by their complex interactions [10]. Among children and young adults, epilepsy contributes more to overall disease burden than any other neurological condition, with 30% to 40% of pediatric patients presenting with co-occurring intellectual disability [8].

Approximately 30% of individuals develop drug-resistant epilepsy, a condition that may result in premature mortality, brain damage, or reduced quality of life [9]. Increased seizure frequency and severity, along with the presence of comorbid conditions, are all linked to diminished HRQoL [11]. Despite notable scientific progress, refractory seizures continue to represent a major clinical challenge, contributing to extensive neurological, cognitive, and psychosocial difficulties. These impairments lead to significant functional limitations and increasing patient dependency, which in turn imposes considerable emotional and practical burden on affected families [12]. Current approaches to the management of refractory epilepsies are centered on three principal therapeutic modalities: pharmacological treatment, surgical intervention, and complementary or alternative options [13]. Despite optimized care, many individuals with epilepsy continue to experience seizures, while others develop adverse effects that limit therapy. These challenges underscore the need for additional drugs and innovative strategies aimed at epilepsy prevention [14].

*History of the ketogenic diet*

Fasting and various dietary interventions have been employed in the management of epilepsy since the Hippocratic period (460-370 BC). In an effort to reproduce the metabolic state induced by fasting, clinicians in the 1920s introduced the ketogenic diet (KD) as an antiepileptic therapy, following early scientific observations that seizure severity diminished during periods of caloric deprivation [15,16]. For approximately two decades, this dietary approach enjoyed broad clinical use; however, its application declined sharply with the advent of contemporary antiepileptic pharmacotherapy. By the close of the twentieth century, availability of the ketogenic diet had become limited to only a small numbers of pediatric hospitals [15]. Over the past decade, global interest in ketogenic diet therapies (KDTs) for drug-resistant epilepsy (DRE) has risen substantially, driven in part by estimates indicating that roughly 19,5 million individuals with epilepsy continue to experience inadequately controlled seizures despite medication. In recent years, more adaptable and less restrictive ketogenic diet variants have been developed to enhance tolerability, improve palatability, minimize side effects, and thereby broaden access for a wider population of patients with refractory epilepsy [16,17]. Evidence from both retrospective and prospective observational studies demonstrates the treatment's effectiveness: more than half of pediatric patients receiving the diet achieved greater than a 50% reduction in seizure frequency, and many became seizure-free within just three months [18].

**Epidemiology of Drug-Resistant Epilepsy in Pediatric Patients**

Epidemiological research on epilepsy typically relies on two core measures: incidence and prevalence [10]. Across observational studies of drug-resistant epilepsy (DRE) published between January 1980 and July 2015, the criteria used to define DRE showed considerable variability, with only 12% of studies adhering to the ILAE definition. The pooled prevalence proportion of DRE among patients with epilepsy was estimated at 0.30. A substantial share of newly diagnosed epilepsy cases occurs in individuals younger than 18 years. Among pediatric patients, the pooled incidence proportion was 0.15 [19,20]. Approximately one in every 150 children receives an epilepsy diagnosis during the first decade of life, with the highest incidence observed during infancy [21].

**Etiology of Drug-Resistant Epilepsy in Pediatric Patients**

Several non-pharmacological approaches - including epilepsy surgery, the ketogenic diet, and various neurostimulation methods - can reduce seizure burden in some individuals with drug-resistant epilepsy (DRE) [22]. Etiology is classified into six categories because each may have therapeutic implications. From the first seizure, clinicians are encouraged to pursue determination of the underlying cause, typically beginning with neuroimaging - preferably MRI - to assess for structural abnormalities. The remaining etiological groups include genetic, infectious, metabolic, immune, and an undetermined category. A single patient may fall into more than one group, as these categories are non-hierarchical and their relevance depends on the clinical context [23]. In pediatric DRE, cohort studies confirm that structural etiologies account for a substantial proportion of cases, followed by genetic causes, while immune and metabolic origins are less common. Importantly, many children still have no identifiable cause, underscoring the need for advances in molecular and genetic diagnostics. The distribution of etiologies also varies by age: genetic causes predominate in infants under one year of age, whereas structural etiologies are most frequent in children aged six years and older [22].

**Structural etiologies**

A structural etiology is defined as an abnormality identifiable on structural neuroimaging that, when correlated with electro-clinical findings, can reasonably be considered the source of a patient’s seizures. Such causes may by acquired or genetically determined [23]. Focal cortical dysplasia represents a malformation arising from abnormal cortical development and accounts for nearly half of drug-resistant epilepsy cases in pediatric population. Despite its significance, it remains insufficiently recognized and is still infrequently diagnosed in Poland [24].

## Pathophysiology of Drug-Resistant Epilepsy

The pathophysiology of drug-resistant epilepsy (DRE) remains only partially understood. Numerous investigations employing both in vivo and in vitro approaches have outlined several major conceptual models, including the drug-transporter hypothesis, neural-network hypothesis, drug-target hypothesis, genetic-mutation hypothesis, disease-severity hypothesis, and pharmacokinetic hypothesis. Each of these frameworks, however, carries intrinsic limitations and areas of overlap [22]. Recent experimental research has further examined potential mechanisms underlying refractory epilepsy, highlighting two predominant explanations for the failure of antiepileptic drug (AED) therapy: the transporter hypothesis and the target hypothesis. The former posits that AED inefficacy results from upregulated multidrug transporters that lower drug concentrations at their intended sites to subtherapeutic levels. The latter suggests that, in some patients, structural or functional alterations in drug targets render AEDs less effective [13]. Neuroinflammatory processes can disrupt the integrity of the blood-brain barrier, lead to neuronal injury, and enhance neuronal excitability. These changes not only precipitate epileptic activity but also show a strong association with the development of DRE. There is evidence that pro-inflammatory mediators contribute to intrinsic disease severity and can additionally modulate both pharmacokinetic and pharmacodynamic properties of AEDs [22,25]. The mechanisms implicated in DRE, as outlined above, may by modified by numerous factors and are subject to regulation at multiple biological levels. These include genetic and epigenetic influences, as well as other endogenous modulators such as inflammatory cytokines and metabolic factors [25].

## Ketogenic diet

Due to the substantial rate of treatment discontinuation, several more palatable and tolerable versions of ketogenic diet have been developed to minimize adverse effects and enhance adherence and patient satisfaction. Currently, the following ketogenic diet variants are available (Figure 1):

1. The classic ketogenic diet (cKD)
2. A modified Atkins diet (MAD)
3. A low glycemic index treatment (LGIT) [26].

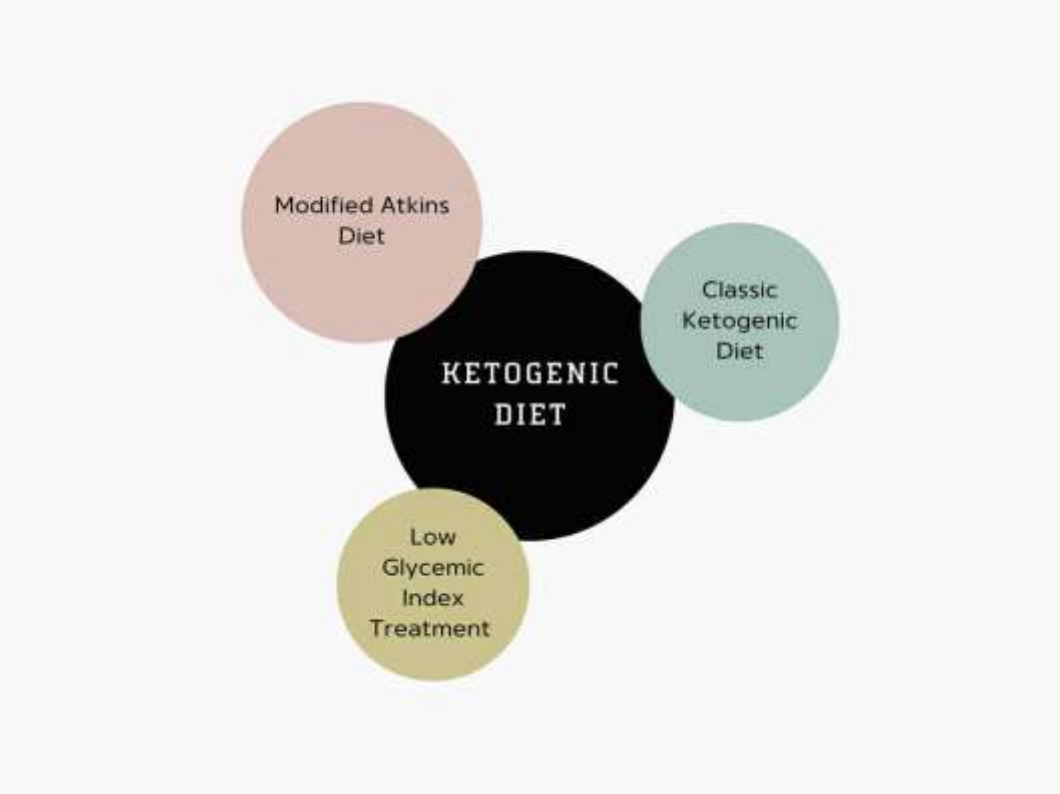


**Figure 1. Different variants of the ketogenic diet.**

*Understanding the Ketogenic Diet and Ketogenesis*

The ketogenic diet (KD) is a low-carbohydrate, high-fat dietary regimen. This leads to a shift in metabolic state. KD was defined as a diet that induces ketosis [27,28].

At the onset of ketogenic diet, blood glucose levels decline and the body enters a catabolic state. The primary metabolic pathway utilized is glycogenolysis, which involves the breakdown of glycogen in skeletal muscle and the liver. Once glycogen stores are depleted, the body produces glucose from non-carbohydrate substrates (lactate, amino acids) through the process of gluconeogenesis [29]. With prolonged low carbohydrate availability, metabolism is redirected toward the utilization of fatty acids as the main energy substrate. This occurs because reduced blood glucose concentrations lead to decreased insulin levels, which in turn increases the concentration of free fatty acids (FFA) due to diminished inhibition of hormone-sensitive lipase [27]. The increase in FFA and the low glucose concentration activate the ketogenic pathway, which produces ketone bodies that serve as an alternative energy source for the organism. Ketogenesis results in the formation of acetone, acetoacetate, and β-hydroxybutyrate. This process occurs primarily in the mitochondria of the liver. Free fatty acids are transported into

the mitochondria by carnitine palmitoyltransferase-1 (CPT-1), and subsequently are degraded to acetyl-CoA through β-oxidation. Two molecules of acetyl-CoA are converted by thiolase into acetoacetyl-CoA. Acetoacetyl-CoA is then transformed into acetoacetate through two consecutive reactions. β-hydroxybutyrate is produced from acetoacetate in a reaction catalyzed by β-hydroxybutyrate dehydrogenase [30]. The resulting ketone bodies are released from the liver into the systemic circulation and transported to extra hepatic tissues. In the mitochondria, BHB and acetoacetate are utilized to regenerate acetyl-CoA, which is then incorporated into the Krebs cycle [27]. Under physiological conditions, the brain relies primarily on glucose for ATP production. When glucose availability is limited, ketone bodies become the main fuel for the central nervous system. The transport of ketone bodies across the blood-brain barrier (BBB) depends on monocarboxylate transporters (MCTs). Several isoforms of these transporters exist, but neurons predominantly express the MCT2 isoform, which has a high affinity for BHB. The rate of ketone body uptake depends on their concentration in the blood [31].

**Classical Ketogenic Diet**

The classical ketogenic diet (cKD) is a high-fat, low-carbohydrate dietary regimen. It is defined by a standard fat to carbohydrate plus protein ratio of 4:1 by weight. For patients following this diet, total caloric intake is typically reduced to 80-90% of the estimated daily energy requirement. Under these conditions, approximately 90% of total energy is supplied by long-chain fatty acids, whereas only about 10% is derived from carbohydrates and proteins. There are two approaches to initiating dietary intervention: the classic method and the alternative method. In the classic method, hospitalization is required. The intervention begins with a fasting period lasting between 12 and 72 hours. Following this, patients are gradually introduced to meals of increasing caloric density until full tolerance of a complete caloric intake is achieved. The alternative method reduces the risk of fasting-related adverse effects (acidosis, weight loss, hypoglycemia) because it involves the progressive increase of the fat to carbohydrate plus protein ratio (start at 1:1, then 2:1, and ultimately reaching 4:1), while maintaining full caloric intake rather than the reduced intake used in the classic method [32]. This dietary therapy is the most restrictive among the ketogenic diet variants, and adherence may be challenging. In cases of poor tolerance or the emergence of adverse effects, lower ratios such as 3:1 or 2,5:1 can be implemented as an alternative [33].

Numerous scientific publications provide strong evidence supporting the efficacy of the ketogenic diet in the pediatric population.

In 2008, Neal et al. conducted a 3-month randomized controlled trial evaluating the ketogenic diet (KD) in pediatric drug-resistant epilepsy (DRE). Children experiencing at least seven seizures per week were enrolled and allocated to either the KD or control group. The KD arm demonstrated a 75% greater reduction in seizure frequency compared with controls. 38% of participants achieved a reduction exceeding 50%, and 7% experienced a reduction greater than 90%. Adverse events were reported in approximately 25% of children, most commonly constipation, followed by vomiting, diarrhea, and taste disturbances [18].

A 2017 randomized controlled trial by Lambrechts et al. evaluated children and adolescents aged 1-18 years with DRE who were assigned either to a ketogenic diet or to standard care (CAU). After four months, at least a 50% reduction in seizure frequency was observed in 50% of participants on the ketogenic diet, compared with 18.2% in the control group. The most frequently reported adverse effects were gastrointestinal symptoms, including vomiting and constipation. The authors concluded that the KD is an effective and well-tolerated treatment for DRE [34].

A pragmatic, real-world clinical study conducted at the Amrita Institute of Medical Sciences in Kochi inducted children aged 0-18 years with DRE. Before starting the diet, 52 of 74 children experienced more than five seizures per day. After an average of 10.4 months on the ketogenic diet, 59.4% achieved a seizure reduction exceeding 50%, 25 children (33.7%) experienced a reduction greater than 90%, and 6 children (8.1%) became completely seizure-free [35].

Another study, a retrospective cohort analysis conducted in Bahrain, included 24 children treated with classical ketogenic diet. After six months, 58.3% achieved a seizure reduction above 50%, and after 12 months, 33.3% became completely seizure-free. The main limitations of this study were its small sample size and retrospective design [36].

**The Low Glycemic Index Treatment (LGIT)**

The Low Glycemic Index Treatment (LGIT) was developed in 2002 by Dr. Elizabeth Thiele and dietitian Heidi Pfeifer at Massachusetts General Hospital in Boston. Its purpose was to offer patients a more flexible dietary alternative to the traditional ketogenic diet. The first study demonstrating its effectiveness was published in 2005 [37]. The LGIT allows the consumption of 40-60 g of carbohydrates per day, but these must be carbohydrates with a low glycemic index (<50). It is essential to exclude carbohydrates with a high glycemic index from diet [38]. The glycemic index (GI) reflects the extent to which specific food raise blood glucose levels after consumption, with ingested glucose serving as the reference value of 100. The LGIT is typically initiated in an outpatient setting [29]. Studies conducted on adult rats have demonstrated that

high glucose concentrations correlate positively with seizure susceptibility [39]. Rapid fluctuations in blood glucose and insulin levels may precipitate seizures in patients with epilepsy. The primary objective of the LGIT is to maintain relatively stable blood glucose concentrations and to prevent substantial postprandial insulin surges [29]. An important advantage of the LGIT is the relative ease of meal preparation, as neither meticulous planning nor precise portion weighing is required. This may enhance dietary adherence and, consequently, improve treatment effectiveness [40].

An open-label, randomized controlled trial with two parallel arms was conducted between 2011 and 2012 in New Delhi. Children older than 2 years with drug-resistant epilepsy were randomly assigned either to the LGIT group or to the control group. Participants in the LGIT arm received a low-glycemic index diet for an additional 3-month period. Each group consisted of 20 children. In the LGIT group, 6 of 20 children achieved a seizure reduction of greater than 50%, whereas none of the 20 children in the control group reached a reduction exceeding 50% [41].

A 2024 meta-analysis included 13 studies published between 2005 and 2021. The duration of dietary intervention in the included studies ranged from 6 to 58 weeks, and the age of participants spanned from 2 to 13,1 years. The pooled efficacy rates for <50%, ≥50%, and >90% seizure reduction among epilepsy patients receiving a low glycemic index diet were 39%, 34% and 19%, respectively [42].

The primary reason for discontinuation of the low glycemic index treatment (LGIT) in children with drug-resistant epilepsy is the dietary restriction it entails. Although LGIT is the least restrictive of the ketogenic diet variants, parents frequently encounter challenges with sustaining the diet over longer periods [43].

The aim of one study was to compare the effectiveness of daily versus intermittent LGIT in children with DRE after 24 weeks of dietary treatment. Children in the intermittent group received a liberalized diet on two days per week, during which medium-glycemic index food were permitted, and carbohydrates could comprise up to 20% of daily caloric intake. After 24 weeks, the mean weekly reduction in seizure frequency was comparable between the intermittent and daily LGIT groups. Additionally, the burden of care was lower in families following the intermittent LGIT regimen [43].

**Modified Atkins Diet (MAD)**

The Modified Atkins Diet (MAD) was developed in 2006 at the Johns Hopkins Hospital in the United States. MAD is a dietary therapy characterized by a strict daily carbohydrate limit (10-20 g) combined with a high intake of fat, with the objective of achieving seizure control. This dietary approach typically provides a ketogenic ratio of 1:1 or 2:1 [44]. The macronutrient composition of the diet consists of approximately 65% fat, 25% protein, and 10% carbohydrates, which enhances its palatability compared with more restrictive ketogenic regimens [45]. Meal preparation is considerably simpler with MAD, as food items do not need to be precisely calculated and weighed on a gram scale, in contrast to the classical ketogenic diet [44].

**Comparison of Dietary treatment Efficacy**

Numerous clinical studies have been conducted comparing the cKD, MAD and LGIT in children with drug-resistant epilepsy. The findings of these studies are presented below.

**cKD vs MAD**

A prospective, randomized clinical trial (RCT) conducted in South Korea demonstrated significant improvement in children with DRE. After 3 months, the mean seizure frequency was reduced to 38,6% of baseline in the KD group and to 47,9% in the MAD group. After 6 months, seizure frequency decreased to 33,8% (KD) and 44,6% (MAD). Among patients younger than 2 years of age, 53% were seizure-free after 3 months on the KD, compared with only 20% in the MAD group [46].

In 2017-2018, a study conducted in Iran compared the effectiveness of the KD and MAD over a 6-month period in children aged 2-15 years. Approximately 45,8% of children in the KD group and 45,5% in the MAD group achieved a ≥50% reduction in seizure frequency [47].

A study conducted at Menoufia University Hospital in Egipt evaluated the short and long term efficacy of cKD and MAD over a 24-month period. Both the classical KD and the MAD proved effective: seizures ceased in 60% of children in the cKD group and in 50,33% of those in the MAD group. Among the remaining patients, a ≥ 50% reduction in seizure frequency was observed. The study also assessed EEG changes, demonstrating improvement in background rhythm and a reduction in interictal epileptiform discharges (IEDs) in both groups [48].

**MAD vs LGIT**

In a randomized non-inferiority trial by Ananda et al. (2025), the efficacy of the LGIT was compared with the MAD in children with DRE. After 24 weeks, seizure reduction was

comparable between the two groups (MAD 60,7% vs. LGIT 57% ; p=0,664). Adverse events were more frequent in the MAD group, particularly dyslipidemia and issues with dietary tolerance. LGIT demonstrated efficacy similar to that of the MAD, while offering a more favorable safety profile, supporting its use as an alternative dietary therapy in children with DRE [49].

**cKD vs MAD vs LGIT**

In 2020, the All India Institute of Medical Sciences in New Delhi conducted the first direct randomized trial comparing all three diets. The intervention period was 24 weeks, and the median change in seizure frequency was as follows: KD -66%, MAD -45%, and LGIT -55%. The proportion of children achieving a ≥ 50% reduction in seizures was 67,3% for the KD, 51,9% for the MAD, and 59,3% for LGIT. This study demonstrated that the classical KD is more effective than both the MAD and the LGIT. The incidence of adverse events was comparable between the KD and MAD groups, with the lowest rate observed in the LGIT group [50].

**Mechanisms of the Ketogenic Diet**

The ketogenic diet exerts multifaceted effects on the nervous system. Its neuroprotective properties have been well documented in epilepsy, neurodegenerative disorders, traumatic brain injury, and autism spectrum disorder. The antiepileptic effect of the KD results primarily from the actions of ketone bodies, which modulate synaptic transmission and limit excessive, pathologically enhanced neuronal activity. Metabolites generated during ketogenic metabolism reduce oxidative stress and the seizure-inducted inflammatory response. These effects arise from several overlapping mechanisms [51].

**1.Effects on the GABAergic System**

The ketogenic diet increases GABA levels. Gamma-aminobutyric acid (GABA) is the principal inhibitory neurotransmitter, and its enhanced activity is thought to contribute to seizure suppression in patients on the KD. The diet increases the expression of glutamic acid decarboxylase (GAD), thereby enhancing GABA synthesis, and also inhibits GABA degradation [52].

**2. Effects on Glutamatergic Transmission**

Glutamate is the main excitatory neurotransmitter in the central nervous system. Excessive glutamate release can lead to excitotoxicity and neuronal death. Binding of glutamate to NMDA

receptors opens voltage-dependent ion channels, allowing calcium influx and generating action potentials. β-hydroxybutyrate (BHB) exerts inhibitory effects on NMDA receptors, reducing neuronal excitability [51].

**VGLUT modulation**

Ketone bodies, including acetoacetate and β-hydroxybutyrate, modulate the vesicular glutamate transporter (VGLUT), which loads glutamate into presynaptic vesicles. VGLUT contains an allosteric activation site for chloride ions ($Cl^-$). Acetoacetate more strongly than BHB competes with $Cl^-$ at this site, inhibiting VGLUT function and thereby decreasing glutamate release [53].

**3. Effect on ATP-Sensitive Potassium (KATP) Channels**

These channels are octamers composed of four Kir6.2 pore-forming subunits and four regulatory SUR subunits. They are expressed, among other regions, in the hippocampus. Ketone bodies enhance KATP channel activity [54]. This effect likely results from reduced glycolytic ATP levels induced by the ketogenic diet, leading to the opening of KATP channels. The resulting neuronal hyperpolarization decreases neuronal firing and overall excitability [55].

**4. Decanoic Acid and AMPA Receptors**

A medium-chain triglyceride based ketogenic diet increases concentrations of decanoic acid and ketone bodies. Decanoic acid inhibits excitatory neurotransmission by directly blocking AMPA receptors in the brain, contributing to its anticonvulsant properties [56].

**5. Increased Production of Adenosine**

Adenosine is an inhibitory neuromodulator with neuroprotective and anticonvulsant effects. Its levels are regulated by adenosine kinase (ADK), which phosphorylates adenosine to inactive AMP [57]. The ketogenic diet enhances astrocytic and neuronal metabolism, increasing extracellular adenosine. This activates neuronal adenosine A1 receptors, resulting in reduced glutamate release and a subsequent anticonvulsant effect [32].

**6. Effects on Mitochondrial Mechanisms**

Epilepsy induces pathological changes in mitochondrial metabolism and increases the production of reactive oxygen species (ROS). The ketogenic diet improves mitochondrial function, reducing oxidative stress by elevating levels of reduced glutathione (GSH). Decreased ROS production may also result from increased of uncoupling proteins [58]. β-hydroxybutyrate augments mitochondrial respiration, enhances NADH oxidation, and increases ATP production

[59]. Ketone bodies exhibit neuroprotective properties and promote overall mitochondrial health [60].

**7. Effects on the Immune System**

The precise role of ketone bodies in innate immunity remains unclear. B-hydroxybutyrate inhibits NLRP3 inflammasome activation by preventing potassium efflux. It reduces IL-1β and IL-18 production via NLRP3 signaling in monocytes. Evidence suggests that the anti-inflammatory effects of the ketogenic diet may be mediated through this mechanism [61].

**Adverse Effects of the Ketogenic Diet**

Adverse effects associated with the ketogenic diet can by classified as early or late, the latter occurring after approximately three months of therapy. Immediately following the initiation of a ketogenic dietary therapy, gastrointestinal disturbances are the most commonly observed adverse effects. These are primarily due to low fiber intake and the high fat content of the diet, and they generally resolve spontaneously as the body adapts [44]. Kidney stones represent a significant complication of the KD. Chronic metabolic acidosis can lead to hypercalciuria, resulting from reduced renal calcium reabsorption and increased urinary calcium excretion. The risk of kidney stone formation can be mitigated through the administration of oral potassium citrate, which acts as a crystallization inhibitor, increases urinary pH, and promotes calcium solubility [62]. During the acute phase of dietary treatment, hypoglycemia may also occur. Dyslipidemia is another concern, though lipid profiles tend to gradually normalize with continued therapy. Among micronutrient and vitamin deficiencies, calcium and vitamin D deficiencies are most frequently observed, and supplementation is recommended when deficiencies are confirmed [44]. Bone health should be regularly monitored, as ketogenic therapy may reduce bone mineral density, increasing the risk of osteopenia and, eventually, osteoporosis [63]. In patients on long-term ketogenic therapy, the risk of late-onset adverse effects should be considered. One of the most clinically significant concerns is growth impairment, necessitating regular monitoring of growth curves in children [44].

**Conclusion**

The classical ketogenic diet (cKD) has demonstrated efficacy in the management of children with drug-resistant epilepsy (DRE). However, its strict regimen and limited palatability often result in poor adherence and frequent discontinuation. To address these limitations, alternative dietary approaches such as the modified Atkins diet (MAD) and the low glycemic index

treatment (LGIT) have been developed. These interventions offer greater flexibility, improved tolerability, and lower risk of adverse effects. Although generally less potent in seizure control than cKD, they provide a valuable and practical therapeutic option for many patients. Despite these advances, further research is warranted. Long-term, randomized controlled trials and large-scale population studies remain scarce. Moreover, the underlying mechanism of ketogenic diets are incompletely understood, including the roles of ketone bodies, their impact on neuronal activity, modulation of the gut microbiome, and immune system function. Elucidating these processes is essential for optimizing dietary therapies in DRE and may facilitate the development of more effective, better-tolerated strategies.

## Disclosure

### Authors' Contributions:

Conceptualization was done by Jakub Jopek; methodology by Jakub Jopek and Hanna Tymchenko; software by Martyna Świątecka; checking by Jakub Kaźmierczyk; formal analysis by Sylwia Bryksy; investigation by Natalia Popczyk; resources by Ewa Buczkowska; data curation by Michał Popczyk; writing-rough preparation by Aleksandra Marciszewska; writing-review and editing by Jakub Kaźmierczyk; visualization by Jakub Jopek and Sylwia Bryksy; supervision by Agnieszka Przybyłowska; project administration by Aleksandra Marciszewska; All authors have read and agreed with the published version of the manuscript.

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