



# The Effect of Ketogenic Diet Treatment in Drug-resistant Epilepsies of Childhood

## Çocukluk Çağı Dirençli Epilepsilerinde Ketojenik Diyet Uygulamalarının Etkisi

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### Abstract

Epilepsy is an important health issue. The interest in ketogenic diet (KD) treatment in children and adolescents with drug-resistant epilepsy has increased in recent years. It was thought that KD was a last option of treatment in patients who were unresponsive to 2 or 3 anticonvulsant drugs. KD with limited protein, low carbohydrate, and high fat content was thought as a last option of treatment, previously. However, nowadays it is the most selected therapy worldwide in epileptic children and adolescents. Ketone bodies are elevated in the blood due to low carbohydrate and high lipid content of KD. Through the elevation of ketone bodies, the brain uses ketone bodies as energy sources, which results in decreased in epileptic seizures. Medical nutritional therapy during treatment of childhood epilepsies should also provide normal growth and development. For this reason, full compliance with the diet is important. The effect, place, and importance of ketogenic nutrition therapy in drug-resistant epilepsies of childhood are discussed in this review.

**Keywords:** Childhood, drug-resistant epilepsy, ketogenic diet

### Öz

Epilepsi önemli bir sağlık sorunudur. Son yıllarda dirençli epileptik çocuk ve adölesanlarda ketojenik diyet (KD) uygulamalarına olan ilgi giderek artmaktadır. KD 2-3 çeşit antikonvülzan ilaçla nöbet kontrolü sağlanmadığı durumlarda son çare tedavi yöntemi olarak düşünülmektedir. Proteinden sınırlı, düşük karbonhidrat ve yüksek yağ içeriğine sahip KD uygulamaları daha önceleri son çare olarak uygulanırken günümüzde sıklıkla kullanılan bir tedavi haline gelmiştir. Diyetteki karbonhidrat içeriğinin düşük ve yağ içeriğinin yüksek olması nedeniyle kanda keton cisimlerinin artışı söz konusudur. Keton cisimlerinin artışıyla beyin keton cisimlerini enerji kaynağı olarak kullanmakta ve epileptik nöbetlerde azalma görülmektedir. Çocukluk döneminde epilepsi tedavisi süresince yapılan beslenme tedavisi normal büyüme ve gelişmeyi sağlamalıdır. Bunun için de diyete uyumun tam olması oldukça önemlidir. Bu derlemede çocukluk çağı dirençli epilepsilerinde KD'nin etkisi, yeri ve önemi irdelenmiştir.

**Anahtar Kelimeler:** Çocukluk çağı, ilaca dirençli epilepsi, ketojenik diyet

### Introduction

#### Ketogenic Diet

Epilepsy, one of the most common neurologic disorders of childhood, is complicated with pharmacoresistance in one-quarter of all patients. Seizures cause delay cognitive and psychosocial development and prevent reaching normal developmental capacity in children in whom neuronal differentiation is not yet completed (1). Ketogenic diet (KD) is the last treatment option in patients whose seizures are resistant to 2 or 3 anticonvulsant drugs (2).

The classic KD, which was developed in the 1920s, has been effectively used in patients with drug-resistant epilepsy (3). KD

is known as "long chained triglyceride" diet, which has limited protein, low carbohydrate, and high fat content (4). Most of the energy gathered by feeding comes from fats. Protein intake is kept in the lower limit of requirements and carbohydrate intake is severely restricted (5).

The ratio of fat to carbohydrate and protein is determined as 4:1 in terms of grams in the classic form of KD. Ninety percent of the energy is gathered from fats and 10% from carbohydrates and proteins (6). In such a diet, to provide enough protein, ratios of 3:1 (86% fats) and 2:1 (83% fats) are preferred in adolescents, children, and infants. KD is preferred in children aged above 1 year because children aged below 1 year are more prone to hypoglycemia (2).

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KD causes production of ketone bodies in the liver, which is its most important feature. Ketone bodies are used as an alternative fuel to glucose for energy and brain development (7). A decrease in serum glucose levels causes  $\beta$ -oxidation of the fatty acids leading to the production of ketone bodies (acetone, acetoacetate,  $\beta$ -hydroxybutyrate). Ketone bodies take place in brain development, cell membranes, and lipid biosynthesis besides serving as energy substrates (8).

KD is considered as one of the most effective treatment options in epilepsies of childhood (5). The energy and nutrients of a KD should be calculated individually (4). Fluid restriction has not been recommended in recent years because sufficient fluid intake prevents dehydration and plays protective roles against constipation and kidney stone formation (5).

### Indications and Contraindications of the Ketogenic Diet

KD has been used for years in patients who are not appropriate for epilepsy surgery and who are refractory to conventional antiepileptic drugs (9). There are special conditions in which KD can be beneficial and also there are contraindications for KD (5). The indications and contraindications of KD are shown in Table 1 (2). Fat is used as a source of energy instead of carbohydrate in KD, which can cause serious problems if KD is used in disorders of lipid metabolism. For this reason, children should be screened for disorders of fatty acid oxidation and transportation before the initiation of KD (2).

### Mechanisms of Action of Ketogenic Diet

The mechanisms of action of KD are not well known (5) but multiple mechanisms are considered to take place in suppressing seizures (10). These mechanisms are:

**Importance of ketone bodies:** Clinical evaluations of patients who are on KD are performed due to  $\beta$ -hydroxybutyric acid (BHB) levels in serum. Studies have tried to find a causal relationship between ketonemia and the anticonvulsant effect. Although high serum levels of BHB were achieved with KD (7,11), no relationship could be found between BHB levels and seizure control (8). However, in a study performed on mice with Dravet syndrome, higher BHB serum levels were achieved in mice on a KD compared with mice with a standard diet and a better seizure control was achieved in mice on KD (12).

KD with a higher ratio of fat (6:1) was used in mouse models and resulted in better outcomes (ignoring the toxic effects) (13). The modified Atkins diet (MAD) and low glycemic index treatment (LGIT) were shown to have similar effects with KD, but they resulted in less ketosis. High levels of ketosis are not considered as the main mechanism in humans (14,15,16,17).

**Role of polyunsaturated fatty acids (PUFA):** PUFAs including docosahexaenoic acid (DHA) and arachidonic acid are related with cardiovascular functions (7). Recent studies have focused on PUFAs. After KD, serum and brain levels of PUFAs including DHA and arachidonic acid were shown to increase (18). PUFAs are thought to modulate neuronal membrane excitability by

Table 1. Indications and contraindications of the ketogenic diet (2)

Probable benefits (at least two publications)	Absolute contraindications
GLUT-1 deficiency	Primary carnitine deficiency
PDHD	CPT 1 or 2 deficiency
Myoclonic astatic epilepsy (Doose syndrome)	Carnitine translocase deficiency
Tuberous sclerosis complex	<b>Oxidation defects</b>
Rett syndrome	Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
Severe myoclonic epilepsy of infancy (Dravet syndrome)	Long-chain acyl-CoA dehydrogenase deficiency (LCAD)
Infantile spasms	Short-chain acyl-CoA dehydrogenase deficiency (SCAD)
Children only receiving formula (infants or enteral feeding patients)	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
	Medium-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
	Pyruvate carboxylase deficiency
	Porphyria
<b>Possible benefits</b>	<b>Relative contraindications</b>
Some mitochondrial disorders	Difficulty in maintaining adequate nutrition
Glycogenesis type 5	Surgical focus identified by neuroimaging and video EEG monitoring
Landau Kleffner syndrome	Parent or caregiver noncompliance
Lafora's disease	
SSPE	
GLUT-1: Glucose transporter-1, PDHD: Pyruvate dehydrogenase deficiency, SSPE: Subacute sclerosing panencephalitis, CPT: Carnitine palmitoyl transferase, CoA: Coenzyme, EEG: Electroencephalography	

stabilizing voltage-gated sodium and calcium channels (10). Some studies showed higher arachidonic acid levels provide seizure control, whereas others showed no relationship between high level of PUFAs and seizures. The anticonvulsant effects of PUFAs are under research (19,20,21). Fatty acids modulate uncoupled mitochondrial protein expression and activation. Activation of mitochondrial uncoupled proteins causes a decrease in the proton gradient against the inner mitochondrial membrane, which leads to a decrease in the production of free oxygen radicals. A decrease in the production of free oxygen radicals can prevent epileptic activity (22).

**Anti-inflammatory effects and protection from excitotoxicity:** KD has anti-inflammatory effects and provides protection from excitotoxicity-induced neuronal death. Glutamate toxicity in the hippocampus is held responsible for neuronal damage. It is suggested that KD reduces this toxicity (10).

**Neurometabolites and changes in their receptors:** KD affects seizure control by changing neurometabolite levels. In vivo studies have shown that high levels of BHB increase synthesis of cerebral kynurenic acid (endogenous antagonist of glutamate), which has anticonvulsant effects (23). Another study showed that acetoacetate and BHB were affected by increasing transamination of glutamate to aspartate and conversion to gamma-aminobutyric acid (10).

**Positive energy balance:** It was shown that when rats were on KD, total levels of bioenergetic substrates (i.e ATP) were increased and cell membranes were stabilized, which provided protection in conditions requiring high energy such as seizures (10).

**Antioxidant mechanisms:** Ketone bodies prevent formation of free radicals by decreasing coenzyme Q10 levels. Also, ketone bodies prevent lipid peroxidation by increasing the activity of glutathione peroxidase in the hippocampus of rats (10).

### Efficacy of Ketogenic Diet

The efficacy of KD in drug-resistant childhood epilepsies has been shown in retrospective and prospective studies and meta analyses (5,24,25,26,27). Eleven studies regarding the efficacy of KD in children with drug-resistant epilepsy were evaluated in a systematic review. Seizure freedom was achieved in 16% of patients. There was more than a 90% reduction in seizures in 32% of patients and more than a 50% reduction in seizures in 56% of the patients (5). A Cochrane review evaluated 4 randomized and controlled studies (28,29,30,31). The efficacy of KD on seizures was investigated in 289 children and adolescents in these studies. It was concluded that KD reduced the frequency of seizures in short and medium terms in children (25). Nineteen studies including 1084 children (mean age at initiation  $5.78 \pm 3.43$  years) were evaluated in a meta-analysis by Henderson et al. (27). There was >90% seizure reduction in one-third of patients and >50% seizure reduction in half of the patients. A study from China showed that after 3, 6 and 12 months, 35%, 26.2%, and 18.6% of 317 children with refractory epilepsy on KD showed >50% seizure reduction, respectively (32). Keene (26) found that after initiation of KD, 15.6% of patients became seizure free, and there was >50% seizure reduction in 33% of patients. Twenty-seven children with refractory epilepsy were included in a prospective study

from India. Fifty-five percent remained on KD at 6 months, and 37% remained on it at 1 year. Forty-eight percent had >50% reduction in seizures, and four children (15%) were seizure free at 6 months. At 1 year, 37% had >50% reduction in seizures and five children (18.5%) were seizure free (33). In another study, 61 children with refractory epilepsy were given KD; 29 (48%) were responders at 3 months. Two children became seizure free beginning from the second month and stayed seizure free for 2 years. Twenty-four (42%) of the patients were responders at 6 months (34). KD was used in 10 children with refractory focal status epilepticus for 6 months. Seizures stopped in two patients and five patients had a 50-75% seizure reduction within 5-7 days following the onset of the diet. Three patients had a <50% seizure reduction; however, they all had severe adverse events so the diet was discontinued. Seven patients remained on the diet for 6 months to 3 years (mean 1.5 years), in whom the seizures recurred within 4 months, but their quality of life did not worsen (35). In a study, the efficacy of KD in 58 infants <1.5 years of age and 57 children >1.5 years of age were evaluated. The rates of seizure freedom were 34.5% and 32.7% in infants; 19% and 17.5% in children at 3 and 6 months, respectively (36).

KD is shown to be more effective than most antiepileptic drugs and to reduce seizure frequency at least by 50% in half of the patients (4). KD is a good treatment option in refractory epilepsies. Also after discontinuation of KD, recurrence rate of seizures is reduced. However, there insufficient studies to show the effects of KD on health with long-term use (37).

### Preparation Before the Diet

After initiating KD, patients should be monitored and as a result, consulting services are important. By monitoring the laboratory findings, the nutrition program should be edited (Table 2). KD has to be initiated after training the family. Patients with epilepsy with unknown etiology should be screened for metabolic diseases and families should be informed and checked for kidney stones, which are possible complications of KD. Adapting the diet is very important and all family members (including siblings and elders such as grandmothers) should be trained (4). Dietitians/nutritionists should determine the patient's daily energy and nutrient needs by reviewing the anamnesis of the patient's growth and nutrition. Children with severe neurologic impairment should be evaluated for swallowing and chewing abilities and gastroesophageal reflux (5). The diet should be prepared by considering the family's food preferences, socio-cultural and economic status. Drugs containing carbohydrates should be replaced with carbohydrate-free treatments (4). Several tests are suggested before starting KD (Table 2) (2).

### The Initiation of the Ketogenic Diet

The dietitian and the physician should determine the composition of the diet, the content of liquid, the energy and the ratio of KD. Before initiating KD, a careful anamnesis should be taken. The main protocol of KD is to start with fasting (4). Carbohydrate intake should be limited on the day before initiating

ketogenic feeding (38) and low carbohydrate intake should be achieved for 24 hours. Children should be examined when they are admitted to the clinic and the fasting period should be initiated in the evening (39).

In the initiation of ketogenic feeding, the patient’s serum level of glucose should be checked every 6 hours and the patient should be allowed to drink water. If serum glucose levels decrease to the level of 25-40 mg/dL and the patient is not symptomatic (severe lethargy or vomiting), then no treatment is recommended (4,38). If the patient becomes symptomatic, 30 mL of orange juice is given and serum glucose levels are checked (4). For the initiation of ketogenic feeding, the most common used protocol in the world, The Johns Hopkins Medical Institution’s protocol, should be used. According to this protocol;

1. day; while fasting continues at hospital, fluids are restricted to 60-75 cc/kg. Blood glucose is monitored every 6 hours, carbohydrate-free drugs are used and parents begin an educational program.

2. day; dinner is given as “eggnog” as a third of calculated diet meal. Blood glucose checks are discontinued after dinner. Parents begin to check urine ketones periodically.

3. day; breakfast and lunch are given as a third of diet. Dinner is increased to two-thirds (still eggnog). Education program is completed.

4. day; breakfast and lunch are given as two-thirds of diet allowance. Dinner is first full ketogenic meal (not eggnog).

5. day; full KD breakfast is given. Prescriptions are reviewed and follow-up is arranged. Child is discharged to home (39).

Fasting for 36 hours or ketone positivity in urine should be achieved. On the first day of ketogenic feeding, one-third of the total energy; on the second day two-thirds of the total energy, and on the third day, all of the energy should be provided. Patients can be discharged on the fifth day (4,38).

Bergqvist et al. (40) showed that there was no need to start KD with fasting in children. They showed performing KD gradually reduced the frequency of seizures and reduced adverse

Table 2. Recommendations for pre-ketogenic diet evaluation\* (2)

Counseling	Nutritional evaluation
Discuss seizure reduction, medication, and cognitive expectations	Baseline weight, height, and ideal weight for stature
Identify potential psychosocial barriers to the use of ketogenic diet	BMI when appropriate
Review anticonvulsants and other medications for carbohydrate content	Nutrition intake history: 3-day food record, food preferences, allergies, aversions, and intolerances
Recommend family read parent-oriented ketogenic diet information	Establish diet formulation if it is necessary: oral, enteral or a combination
<b>Laboratory evaluation</b>	Decision on which diet to begin (MCT, classic, modified Atkins, or low glycemic index)
Complete blood count	Calculation of calories, fluid, and ketogenic ratio (or percentage of MCT oil)
Electrolytes to include serum bicarbonate, total protein, calcium, zinc, selenium, magnesium, and phosphate	Establish nutritional supplementation products based on dietary reference intake
Serum liver and kidney tests (including albumin, AST, ALT, BUN, creatinine)	<b>Ancillary testing</b>
Fasting lipid profile	Renal ultrasound and nephrology consultation (if a history of kidney stones)
Serum acylcarnitine profile	EEG
Urinalysis	MRI
Urine calcium and creatinine	Cerebrospinal fluid (if no clear etiology has been identified)
Anticonvulsant drug levels (if applicable)	ECO if history of heart disease
Urine organic acids	
Serum amino acids	

BMI: Body mass index, MCT: Medium chain triglyceride, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, BUN: Blood urea nitrogen, ECO: Echocardiogram, EEG: Electroencephalography, MRI: Magnetic resonance imaging

\*Parameters that should be checked at least once every three months in the first year of the implementation of ketogenic diet

events. They also showed that starting KD gradually without fasting provided easier implementation of KD, shorter periods of hospital stay, and lower expenses. Without fasting, all of the energy can be provided by 1:1 (fat: carbohydrate + protein) KD initially and ratios can be increased daily to 2:1, 3:1 and finally 4:1 (4). On the other hand, starting KD with fasting has important advantages. Fast onset causes production of ketone bodies faster and has advantages in determining what is behind the metabolic disorder. Patients must be hospitalized if fasting will be used and families can be trained to perform KD during their stay at hospital (41). Some authors think that a decrease in frequency of seizures initially, mimics the response to an intravenous loading dose of an anticonvulsant drug (38). The disadvantages of fasting are physiologic stress, risk of hypoglycemia and dehydration, improper hospital conditions, increased expenses, and repeated blood tests. 'Intermittent fasting' was used with KD in pediatric patients in whom seizures were not well controlled and a temporary improvement in the frequency of seizures was reported (42).

### Calculation in Classic Ketogenic Diet

In KD treatment, while calculating individual energy and nutrient demands, ketosis should be maintained but also growth and development should be achieved. A high energy-containing diet causes a rapid increase in weight, whereas a low energy-containing diet results in insufficient ketosis and growth retardation. Fast increases and decreases in weight should be avoided (43). When energy need is being calculated, food consumption records, body weight, height, physical activity status, seizure frequency, and drug use should be considered (6). When calculating daily energy need in children, "weight to height" is the main parameter. If the child has low weight, the current body weight should be used as the initial target of energy. If the child is overweight, then a calculation with a value that is close to "height to weight" is more accurate (43).

### Determining the Ketogenic Diet Ratio

The ratio of KD means the ratio of fats to carbohydrates and proteins (43). It is 3:1 KD in adolescents and infants, in other childhood periods, 4:1 KD are used initially (44). To support protein needs in children aged below 2 years who have a high speed of growing and adolescents, KD with a low ratio is recommended (43,45). Total energy requirement is divided by energy in a diet unit, and as a result, the daily number of diet units is gathered. Total carbohydrate, protein, and fat levels in grams are calculated

according to the level of daily recommendations and then divided equally into three or four meals. The fourth meal is organized according to the 'snack-liking status' of the patient. In every meal, the ratio of KD should remain constant (10). Ratios of KD are intended to better regulate the degree of ketosis and higher ratios of KD results in better ketosis (43,44,46). Same ratios of KD may result in different ketosis levels even in two individuals with same age and weight due to differences in energy metabolisms (43). A study evaluating the efficacy of different KD ratios included 38 children who were divided into two equal groups. One of the groups received 4:1 KD and the other group received 2.5:1 KD. Seizures were reduced by more than 50% in each group. It was concluded that low-ratio KD was as efficient as high-ratio KD and might have lower rates of adverse events. Seo et al. (31) evaluated the differences between 3:1 and 4:1 KD in children with drug-resistant epilepsy and found a better antiepileptic effect with 4:1 KD. Although children in the 4:1 KD group had remissions, children in the 3:1 KD group tolerated it better due to having fewer gastrointestinal symptoms. Classic KD units are shown below (Table 3) (43).

**Example:** Calculation of total diet unit in a patient who has an energy need of 1300 kcal daily and who is determined to receive 4:1 KD:  $1300/40=32.5$

### Calculation of the Amount of Fat That Needs to Be Taken with the Diet

Multiplication of the total diet units and the ratio of KD gives the amount of fat that needs to be taken with KD in terms of grams.

**Example:** If the total diet units is 32.5 and the ratio of KD is 4:1, then the amount of fat that needs to be taken with KD is  $32.5 \times 4 = 130$  grams (43).

### Calculation of Daily Carbohydrate and Protein Needs

While performing KD, it is important to meet the need for protein, which is used for growth and building tissues. The calculation of protein need is made on a daily receipt index (DRI). The multiplication of total diet units and the ratio of KD gives the total amount of carbohydrate and protein need. If the amount of protein is removed from the total amount of carbohydrate and protein, then the amount of carbohydrate need is calculated.

**Example:** Daily protein need of 7-year-old child who is 23 kg, is:  $23 \text{ kg} \times 0.95 \text{ g/kg (DRI)} = 22 \text{ g/day}$ .  $32.5 \text{ (total diet unit)} \times 1 \text{ (KD$

Ketogenic diet ratios	Energy (kcal) values of each unit	Fats (g) in each diet unit	Carbohydrates + proteins (g) in each diet unit
2:1	22	2	1
3:1	31	3	1
4:1	40	4	1
5:1	49	5	1

ratio)=32.5 g (total amount of carbohydrate and protein). When the protein need of the child is removed from the total amount of carbohydrate and protein, then the daily carbohydrate need is calculated:  $32.5-22=10.5$  g (43).

### Alternatives of Ketogenic Diet

There are different methods that are used to prevent the adverse events of classic KD. Alternative diets including the MAD, medium chain triglyceride (MCT) diet, and LGIT allow more energy, liquid, and protein uptake (5). KDs are shown to be more effective than any new antiepileptic drugs in treating patients with refractory epilepsy. A meta-analysis showed the MAD and LGIT resulted in less ketosis but their efficacies were similar to that of classic KD (10).

### Medium Chain Triglyceride Diet

The MCT diet has been used since 1970 as another source of fat (47). MCTs produce more ketone bodies than long chain triglycerides (LCT) (28,48,49). Carnitine is used in the transportation of long chain fats to mitochondrial membranes; medium chain fats (C:6-12) do not require carnitine. The differences in the metabolism of MCTs result in faster and more oxidation. Number of ketone bodies per energy is higher in MCT-based diets compared with long chain fatty acid diets (50). The calculation is based on the ratio in classic KD, whereas it is through percentage in the MCT diet (48). In the treatment of epilepsy, 60% of energy is provided by MCTs (48,49). High amounts of MCTs cause gastrointestinal adverse events, abdominal cramps, diarrhea, and vomiting in children, which limit its use in children with refractory epilepsy (6,48,49). In studies, 30% of energy is provided by MCTs and another 30% is provided by LCTs. It was shown that 40-50% of the total energy need should be provided by MCTs for better gastrointestinal tolerance and ketosis (6,49,51). MCTs can be given as fat or emulsion liquid in diet. MCTs can be included in all meals and snacks. Its mixture with milk facilitates its consumption. MCTs can be included in jellies, soups, mashed potatoes, sauces, and pastries. Consumption of mixtures of MCTs and milk before sleeping can help ketosis at night (6).

Usually, 10% of energy comes from proteins and 15-19% from carbohydrates (49). Neal et al. (29) compared KD and MCT diets in a randomized and controlled study. No difference was found between 45 children who received the classic KD diet and 49 children who received the MCT diet (45% were patients with refractory epilepsy) for 3, 6 and 12 months. Patients with seizure reduction rates more than 50% and 90% were similar without significant difference between the groups. In another study, 16 children with refractory epilepsy received the MCT diet and seizure rates reduced by more than 50% in 64.3% of the children, and 28.6% of the children became seizure free (52).

The MCT diet allows more carbohydrate intake, and as a result, it has more taste compared with the classic diet. Also, the MCT diet allows consumption of more types of vegetables and fruits and larger portions compared with classic KD. Consumption of various and multiple foods results in less micronutrient need and better growth in children compared with KD. Also, kidney stones, hypoglycemia, ketoacidosis, constipation, low bone mineral density, and growth retardation are less frequently seen with the MCT diet. However, the MCT diet is more expensive than classic KD (4,53).

### Modified Atkins Diet

The MAD was developed at the Johns Hopkins Hospital as being less limiting and allows more taste than classic KD (54). MAD allows higher lipid intake and limits carbohydrate intake (55). Protein and energy intake are not limited in MAD, unlike in classic KD (48,55). Fasting is not required at initiation. The contents of MAD are: 60% lipid, 30% protein, and 10% carbohydrate (55). There is no need to plan or limit meals (55,56). Carbohydrate limitation is 10 g/d at initiation, then 15 g/d the next month, and up to 20-30 g/d due to seizure control and toleration (56). The ketogenic ratio in MAD is 0.9:1 (fat: carbohydrate + protein), which is lower than classic 4:1 KD. MAD was used for the first time in 20 children with refractory epilepsy and seizures were reduced in 13 by more than 50%, and in 7 by more than 90% (57). In another study, MAD was used in 32 children with refractory epilepsy for one month and seizures were reduced in 24 by more than 50%, and in 11 by

Table 4. Comparison of four major ketogenic diet plans often used in clinics (1000 kcal/day) (5)

Types of ketogenic diet	Fat (g)	Protein (g)	Carbohydrate (g)
<b>Classic long chain triglyceride diet</b>			
4:1	100	17	8
3:1	96	18	14
2:1	92	20	26
1:1	77	37	40
MCT diet	78	25	50
Low glycemic index diet	67*	40-60*	40-60
Modified Atkins diet	72*	68-78*	10-20

\*Approximate values, MCT: Medium chain triglyceride

more than 90% (58). Very few adverse events were reported because MAD and LDL cholesterol levels were not increased in the pediatric and adult patients in the Johns Hopkins Hospital (30,57). Blood urea nitrogen levels are elevated due to high protein intake but there is no elevation in serum creatinine levels (59). There is still uncertainty about the efficacy of MAD and more studies are needed (56).

### Low Glycemic Index Diet

The LGI diet was used in 2005 for the first time in epilepsy (15). Carbohydrate intake is restricted to 40-60 g/d, 60% of the energy is gathered from fat and 20-30% from protein (48). The glycemic index of all carbohydrates in the meal is kept below 50 (48,49). The ratio in the LGI diet is similar to 1:1 KD (15). Specific meal plans are not arranged and recommendations are made according to individual choices. The distribution of protein, carbohydrate, and fat in meals and meal samples should be arranged by a dietitian (15,48). Nutrients with a high glycemic index (e.g., watermelon, potatoes) cause significant elevation in blood glucose levels, whereas nutrients with LGIT (apple, cucumber, full-grain bread) lower postprandial glucose and insulin levels (60). In a study, 76 children were given an LGI diet for 1, 3, 6, 9 and 12 months. Seizures were reduced by more than 50% in 42%, 50%, 54%, 64%, and 66% of the children, respectively (61). In another study, seizures were reduced by more than 90% in half of 20 children with refractory epilepsy who were given the LGI diet (15). Easy meal preparation, no need for detailed planning for meals, and no need to calculate the portions by grams make the LGI diet feasible. The low fat and free carbohydrate content make the LGI diet more tasty. Patients outside home can reach food without mandatory choosing of special meals, which causes less psychosocial problems (61). A comparison of the four major KD plans most often used in clinics is shown in Table 4 (5).

### Supplement Use in Ketogenic Diet

Only balanced nutrition can provide intake of sufficient vitamins and minerals, but in a KD, intake of vegetables, fruits, enriched grains, and calcium-containing nutrients is limited. Vitamin B supplementation is needed in particular (62). Calcium intake with foods is reduced and vitamin D levels are decreased in KD. Vitamin D and calcium supplementations are needed. Use of multivitamins and minerals that do not contain or only contain very few carbohydrates are advised (5,62). Carnitine supplementation, which may cause serious systemic complications including secondary hypocarnitinemia, cardiomyopathy, and hepatitis, is controversial in most centers (63). More studies on the effects of carnitine supplementation in KD are needed (2).

### Adverse Events of the Ketogenic Diet

There are some adverse events related with KD, which are reported at initiation of the diet or during the diet. Dehydration can be seen at the initiation of the diet. During fasting, low blood glucose levels are usually asymptomatic. If low blood glucose

levels cause symptoms, 30 cc orange juice can be given and glucose levels are followed. Vomiting is common at initiation of the diet (4).

KD is an important factor that causes growth retardation in children. Weight gains and heights are reported below expected values in children who receive this kind of diet (64). Growth requires sufficient energy intake. If the protein/energy ratio is kept at level of 1.5 g/100 kcal, growth retardation can be avoided (65).

Gastrointestinal dysmotility is another adverse event of KD. H2 receptor blockers and proton pump inhibitors can be used for gastroesophageal reflux. Also, families should be informed about the predisposition to constipation and eating vegetables containing multiple fibers, sufficient water intake, and if needed, using laxatives that do not contain carbohydrates are recommended (2).

Kidney stones are seen in 3-10% of patients receiving KD, sufficient hydration prevents the production of kidney stones (66). In cases of hematuria, calciuria or pain, kidney sonography can be performed and creatinine and spot urine calcium are helpful in follow-up. Recent studies showed that oral potassium citrate caused a significant decrease in the prevalence of kidney stones in children receiving KD (3.2-10%) (67).

Serum levels of triglyceride and cholesterol may be increased, especially in the first 6 months of KD and should be followed up (4). Kwiterovich et al. (68) studied the effects of KD on lipid profile and showed that total cholesterol, LDL, VLDL, and triglyceride levels were increased, and HDL levels were decreased at the end of 6 months. Another study showed that KD could be performed successfully in children with hyperlipidemia (69).

Antiepileptic drugs can decrease the absorption of calcium by affecting vitamin D levels and also can cause rickets and osteomalasia by directly affecting bone turnover. KD prevents falls by reducing seizure frequency and also prevents the occurrence of bone fractures by reducing the use of antiepileptic drugs. However, long-term KD may cause a predisposition to osteopenia (70).

Nausea, vomiting, hypoglycemia and lethargy due to severe ketoacidosis can be seen in the acute period of KD, and constipation, weight loss, insufficiencies of vitamins and minerals (vitamin D, Se, Ca), pancreatitis, kidney stones, prolongation of the QT interval, cardiomyopathy, short stature, osteopenia, decrease in albumin and carnitine levels, and abnormalities of lipid profile can be seen in the chronic period of KD (10).

### Use of the Ketogenic Diet in the Future

KD can be neuroprotective in neurologic disorders characterized by neurodegeneration or metabolic disturbances (71). Clinical studies on Alzheimer's disease, amyotrophic lateral sclerosis, migraine, and brain tumors are ongoing (5,72). The use of KD in non-epileptic conditions including otism, bipolar disorder, depression, diabetes mellitus, narcolepsy, obesity, stroke, traumatic brain injury, Parkinson's disease, sleep disorders, and schizophrenia have been reported (5,73). KD has beneficial effects on other neurologic diseases as it has on epilepsy, but the mechanisms of action are not known (74).

## Conclusion and Recommendations

Most patients with epilepsy respond well to pharmacologic treatment, but 20-30% are resistant to antiepileptic drugs. KD reduces seizure frequency of children with refractory epilepsy and has better efficacy than most antiepileptic drugs. Some epileptologists argue that KD is one of the most effective treatments in epilepsies of childhood. Limited meal patterns, supplement need, biochemical findings, and adverse events limit KD's sustainability. Giving education to families is required for a long time and training for feeding is important for the success of the diet. Patients (and their families) who receive KD, should be interested and have a high level of education. Although KD is effective, it is hard for patients and their families to continue the diet because of difficulties in compliance to the diet. Dietitians and neurologists should be aware of KD and increase its use. For potential adverse events, patients should be controlled by dietitians, physicians, and psychologists if needed during treatment. The parents of the patients should be trained for the diet and checked periodically. Also, the limitations of KD are accompanied by psychosocial problems. Eating different foods than peers may cause social isolation. Alternative diet lists should be developed for KD to promote the diversity of foods and facilitate KD's applicability. Future studies are needed to evaluate KD's long-term effects.

## Diet Plan for 1400 kcal and 4:1 Ketogenic Diet

After evaluating the food consumption, body weight and protein needs, a diet that provides 1400 kcal was arranged then a sample menu was prepared for seven-year-old a girl (normal body weight).

### Breakfast

#### Mixed omelette

Egg (42 g)  
Green pepper (26 g)  
Tomato ( 25 g)  
Mushroom (34 g)  
Olive oil (31 mL)

### Lunch

#### Tarhana soup (Traditional Turkish soup)

Tarhana (8 g)  
Tomato (15 g)  
Olive oil (24 mL)  
4:1 ratio unflavored ketogenic formula (15 g)

### Dinner

#### Meat and vegetable saute

Beef (30g)  
Mushroom (19 g)  
Onion (10 g)  
Green pepper (14 g)  
Tomato (20 g)  
Olive oil (33 mL)

### 1 Dec meals

#### Chocolate smoothie

Ketogenic formula in a 4:1 ratio vanilla flavor (32 g)

Cacao (3 g)

Olive oil (12 mL)

Natural sweetener (4 g)

### Ethics

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: G.Ö.U., N.Ş., Design: G.Ö.U., N.Ş., Data Collection or Processing: G.Ö.U., N.Ş., Analysis or Interpretation: G.Ö.U., N.Ş., Literature Search: G.Ö.U., Writing: G.Ö.U.

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