Evaluation of ketogenic diet therapy in children diagnosed with drug-resistant epilepsy: a single-center experience

Gonca Kılıç Yıldırım1, Murat Yağcı2, Anıl Çiğdem Uygur3, Hülya Özen4, Coşkun Yarar5, Kürşat Bora Çarman6

Divisions of 1Child Nutrition and Metabolism, 2Pediatric Neurology and 3Department of Pediatrics Eskisehir Osmangazi University Faculty of Medicine, Eskişehir; Departments of 3Nutrition and Dietetics and 4Statistics, Eskisehir Osmangazi University Faculty of Medicine, Eskişehir, Turkey.

ABSTRACT

Background. We evaluate here the effect of the ketogenic diet (KD) on children with drug-resistant epilepsy (DRE) in terms of clinical effectiveness, anthropometric measurements, and some electroencephalogram (EEG) and biochemical findings.

Methods. Included in the study were 18 children (median age 70 months, 61.1% female) who received the classical KD and modified Atkins diet (MAD) for at least one year due to DRE. The patients’ demographic and laboratory data; weight, height and body mass index values; EEG and electrocardiographic findings; abdominal ultrasonography findings; and biochemical parameters were recorded at baseline and at 12 months after the initiation of the diet. A reduction of ≥50% in the number of seizures was accepted as a response to KD.

Results. Classic KD was chosen for 14 patients (77.8%), and MAD for four patients (22.2%). The response to KD therapy (≥50% reduction) was 55.5% (n = 10) (p = 0.008), and one patient even became seizure-free. By the 12th month of treatment, 10 patients had experienced a reduction of more than 50% in epileptiform discharges, as indicated by EEG findings. There was no difference in seizure reduction between the patients who received classical KD and MAD. A total of 11.1% of the children lost weight during KD treatment. The most common side effect was constipation (n = 10, 55.6%). At the end of one year of treatment, total cholesterol and low density lipoprotein cholesterol (LDL-C) LDL-C levels had increased dramatically, while fasting blood glucose levels had decreased significantly.

Conclusions. Our study suggests that KD treatment provides good clinical efficacy in the treatment of pediatric DRE, and can significantly reduce the frequency of epileptic discharges. Also, total cholesterol and LDL-C levels increased significantly, and fasting blood glucose levels decreased significantly compared to the baseline levels.

Key words: child, classical ketogenic diet, drug-resistant epilepsy, efficacy, modified Atkins diet.

Epilepsy incidence rates in children range from 0.5 to 8 per 1,000 according to population-based research. Nearly, 20–40% of children with seizures fail to respond to medical treatment due to uncontrolled epilepsy or drug resistance.
Ketogenic diets are rich in fat, low in carbohydrates, and contain sufficient amounts of protein, and mimic the effect of fasting on the body.\textsuperscript{10} The use of fasting in epilepsy treatment dates back to the time of Hippocrates, being a nonpharmacological treatment approach to DRE in all age groups, from infancy to adulthood. Recent studies have shown that KD can be applied in children older than six weeks\textsuperscript{11}, and it has been widely used in adolescents and adults, as these patients can more easily follow the diet application and management.\textsuperscript{12,13} International consensus has been reached on the use of KD in DRE, and its positive effects on seizure control, through consensus studies by the International League against Epilepsy (ILAE).\textsuperscript{14} The KD type, application, follow up and management of side effects are the key factors in the use of KD for DRE. In the present study, we evaluate the effect of KD on seizure frequency, anthropometric measurements, EEG results and biochemical findings in children with DRE, whose seizures could not be reduced with two or more AEDs.

**Material and Methods**

The files of the patients followed up at the Pediatric Metabolism and Pediatric Neurology departments of our hospital with the diagnoses of DRE between January 2015 and January 2020 were reviewed retrospectively. Included in the study were 18 children – 11 female (61.1\%) and 7 male (38.9\%) – who had used at least two AEDs and had been receiving KD treatment for at least one year. Demographic data, AEDs used, seizure frequency, type of administered KD, complications and diet efficiency were determined retrospectively from the patients’ files.

The age, gender and ideal weight of the patients were taken into consideration for calculation of energy requirements. For the patients advised to start the KD, a specific diet was prepared for each child on the basis of the food consumed over the previous three days. In accordance with the general principle, the caloric needs of the children were set to 75\% of the recommended energy according to their age and body mass. The children were hospitalized and followed up, and a gradually increasing protocol was applied to these patients without fasting.

The participants’ histories of allergy/food intolerance, dysphagia, reflux and nutritional habits were considered in the selection of the type of diet. Conventional KD is calculated in grams as fat/protein + carbohydrate, with the most commonly used ratio being 4:1 – meaning for every 4 grams of fat, 1 gram of carbohydrate and protein are consumed. Since the protein requirement of infants is higher than that of older children, the classical KD ratio was set as 3:1 (87\% of energy provided by fat). In the older children who were fed enterally, the established diet ratio was 4:1, although each patient’s diet ratio was adjusted according to their ketone level, fasting blood sugar level, seizure frequency and dietary tolerance. The modified Atkins diet was preferred in three adolescent children because it is less restrictive (release of energy and protein intake, etc.) and easier to apply than classical KD and does not need hospitalization, as well as a 68-month boy per the family. The diet ratios for MAD were determined as 1:1 and 1.5:1, and the fluid needs of the children were determined as 1.25–1.5 ml/kcal. The formula KetoCal\textsuperscript{\circledR} (Nutricia) 4:1 was used for all patients, and the fat-to-nonfat (protein plus carbohydrate) ratio in their diet was increased gradually from 0.5:1.0 to 4.0:1.0. Blood ketone levels were measured daily in the first week, twice a week for the next three weeks, and once a week thereafter. The patients’ blood ketone levels were maintained at between 4 and 5 mmol/L, and the target levels were reached in five to seven days. Ketogenic diet was administered for at least three months for the evaluation of its efficacy. All drugs taken by the patients were reviewed for carbohydrate content, and all suspensions were replaced by tablets.
In the study, the cessation of seizures or a ≥50% decrease in the number of seizures was considered a response to the KD. During the diet application, all patients were supported with a low-carbohydrate supplement containing multivitamins and minerals, omega 3 and probiotics.

Weight for age, height for age, weight for height, body mass index (BMI) and fasting blood sugar, total cholesterol, high density lipoprotein cholesterol (HDL-C), LDL-C, triglyceride (TG), calcium, phosphorus, alanine aminotransferase (ALT), aspartate aminotransferase (AST), hemoglobin, blood urea nitrogen (BUN), creatinine, blood gases, thyroid function, electroencephalogram (EEG) findings, echocardiography (ECHO) results, and urinary ultrasonography (USG) values at baseline and at the 12th month of the diet were recorded from the patient files. Dyslipidemia was determined as total cholesterol >200 mg/dl, LDL-C >130 mg/dl, and TG >130 mg/dl. Serum zinc and selenium levels are not measured at our hospital, and are not included in the study.

Ethical approval for the research was obtained from the Ethics Committee of Eskisehir Osmangazi University, Medical Faculty (Dated 12.05.2020, number: 25403353-050.99-E.51610, decision number: 18), and the study was conducted in accordance with the Declaration of Helsinki.

### Statistical analysis

The statistical evaluation of the data was conducted using IBM SPSS Statistics (Version 21.0. Armonk, NY: IBM Corp.). Quantitative variables were expressed as mean±standard deviation or median (Q1–Q3), while qualitative variables were expressed as frequency and percentage. The compatibility with the normal distribution of the differences between the quantitative variables measured at the beginning and at the 12th month of treatment was evaluated with Shapiro–Wilk and Kolmogorov–Smirnov tests. The changes in the variables that followed (or did not follow) a normal distribution between the beginning and the 12th month of treatment were investigated with a Paired samples t-test (Wilcoxon test). The relationship between qualitative variables was analyzed with a Chi-square analysis, where p <0.05 was deemed to indicate statistical significance.

### Result

Included in the study were 18 children (11 female [61.1%]; 7 male [38.9%]) who received classical KD and MAD for at least one year due to DRE. The median age of the children was 70 months (5–192 months). The demographic data of the patients are summarized in Table I. The primary diagnoses of the patients were West syndrome (n = 2), pachygyria (n = 2), Lennox-Gastaut syndrome (n = 1), encephalitis sequela (n = 1), malignant migrating epilepsy (n = 1), Miller-Dieker syndrome (n = 1), Rett syndrome (n = 1), Ohtahara syndrome (n = 1), schizencephaly (n = 1), lissencephaly (n = 1) and hydrocephalus (n = 1). No additional diagnosis was found in the remaining five patients.

| Number (n) | Percentage (%) |
|-----------|----------------|
| Female    | 11 61.1        |
| Male      | 7 38.9         |
| Oral      | 11 61.1        |
| PEG       | 7 38.9         |
| Classical KD | 14 77.8    |
| MAD       | 4 22.2         |
| Number of drugs per day | Number (n) | Percentage (%) |
| 2         | 1 5.6          |
| 3         | 7 38.9         |
| 4         | 3 16.7         |
| 5         | 5 27.8         |
| 6         | 2 11.1         |

PEG: percutaneous endoscopic gastrostomy, KD: ketogenic diet, MAD: modified atkins diet
Of the children participating in the study, 14 (77.8%) used levetiracetam, 12 (66.7%) valproic acid, 10 (55.6%) clobazam and eight (44.4%) vigabatrin. The other AEDs used were topiramate, carbamazepine, clonazepam, zonisamide, phenytoin, phenobarbital and oxcarbazepine. The average number of daily AEDs used by the children was $4\pm1.18$ (min: 2, max: 6) (Table I), and seven patients (38.9%) used three AEDs.

Of the total, 11 patients (61.1%) were fed orally, while seven others (38.9%) were fed through percutaneous endoscopic gastrostomy (PEG). Before starting KD, all patients were evaluated with a tandem mass spectrometry analysis for carnitine metabolism disorders and fatty acid beta-oxidation defects, revealing no contraindications. Considering the needs of the children according to their ages, classical KD was preferred in 14 patients (77.8%), whereas MAD was preferred in four (22.2%) (Table I). In the patients who were on classical KD, 4:1 ($n = 5$) and 3:1 ($n = 5$) ratios were the most common. All KD rates are summarized in Table II.

The mean body weight of the children at the beginning of the diet was $18.30\pm7.45$ kg, and $20.85\pm7.12$ kg at the 12th month, indicating a statistically significant increase was noted in body weight after one year of KD treatment ($p = 0.004$), while two patients (11.1%) experienced weight loss. The average height at the beginning of the diet was $104.96\pm21.05$ cm, and that in the 12th month was $111.65 \pm 21.30$ cm, indicating a significant increase in height measurements ($p = 0.001$). When the yearly growth rates of all patients were analyzed according to their age groups, we found that the annual growth rate of our patients, especially those aged 5-72 months, who had a higher protein requirement, fell behind compared to their age [mean 4.1 cm (2-6 cm)]. The growth in height in four MAD patients was found to be appropriate for their age groups. Table III presents the changes in body weight (kg, SDS), height (cm, SDS), body weight for height (BGVA, %) and BMI (SDS) at baseline and after starting the KD.

The number of seizures in the first year of the diet was compared with the figure from before the diet, and a decrease of more than 50% was noted in 10 patients (55.6%), indicating a statistically significant difference ($p = 0.008$). The seizures ceased completely in one patient (5.55%) who had hydrocephalus secondary to prematurity, while in another patient, the seizures decreased by more than 50% in the first six months, but increased afterwards. While the initial EEG finding of this patient showed epileptic discharges originating from both hemispheres, completely normal EEG findings were reported after sixth month of the diet. The initial EEG findings of three patients were normal; two patients had electrical status epilepticus findings; and the EEG findings of 10 patients showed a decrease of more than 50% in epileptiform discharges at the 12th month of treatment ($p = 0.219$). Myoclonic seizures were initially present every day in two patients on MAD, and the number of seizures reduced to once a week within the first six months of therapy, rising again to three days a week. In the two other patients who received MAD, the length of the seizures reduced, and the patients’ social skills improved. There was no difference in seizure responsiveness of those on the classical KD and MAD. A comparison of the classical KD patients on different diet ratios revealed no significant difference in the number of seizures ($p = 0.380$). More than 50% reduction in the number of seizures was 62.3% in patients using three or less AEDs, compared to 50% in those using four or more AEDs ($p = 0.664$). The EEG findings of five patients using three or less AEDs (%62.5) and seven patients using four or

| Table II. Classical ketogenic diet ratios of patients. |
|-----------------------------------------------|
| **Classical KD rate** | **Number (n)** | **Percentage (%)** |
| 4:1            | 5            | 35.7        |
| 3:1            | 5            | 35.7        |
| 2.5:1          | 2            | 14.3        |
| 2:1            | 1            | 7.1         |
| 3.5:1          | 1            | 7.1         |
| Total          | 14           | 100         |

KD: ketogenic diet
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Ketogenic Diet in Drug Resistant Epilepsy

The most common dietary side effect in our study was constipation (n = 10, 55.6%), and no nausea, vomiting, infection or hepatic side effects were observed. The distribution of side effects experienced during the diet is presented in Table V. Echocardiogram evaluations of the patients at the beginning and at the 12th month of treatment were normal. Of the 14 patients with urinary USG reports, nephrolithiasis was detected in one patient at the beginning of the

more AEDs (%70) showed a decrease of more than 50% in epileptiform discharges (p = 1.00) (Table IV).

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Table III. The difference between anthropometric measurements of patients between baseline and 12th month of treatment.

|                          | Mean ± S.D. | Median | (Min)-(Max) | P     |
|--------------------------|-------------|--------|-------------|-------|
| Weight for age (kg)      |             |        |             |       |
| 0.month                  | 18.3 ± 7.45 | 16.85  | (7.2)-(34)  | 0.004*|
| 12.month                 | 20.85 ± 7.12| 21     | (8.8)-(31.5) |       |
| Weight for age (SDS)     |             |        |             |       |
| 0.month                  | -1.34 ± 3.19| -0.75  | (-11)-(2.97) |       |
| 12.month                 | -1.07 ± 2.32| -0.84  | (-6.61)-(3.53) | 0.816*|
| Height for age (cm)      |             |        |             |       |
| 0.month                  | 104.96 ± 21.05| 110.5 | (62)-(136)   |       |
| 12.month                 | 111.65 ± 21.30| 114.25| (76)-(145)   | 0.001**|
| Height for age (SDS)     |             |        |             |       |
| 0.month                  | -0.94 ± 2.3 | -0.83  | (-5.85)-(2.75) |       |
| 12.month                 | -1.12 ± 1.66| -1.25  | (-4.38)-(2.11) | 0.522*|
| Weight for height (%)    |             |        |             |       |
| 0.month                  | 97.59 ± 14.39| 96.93 | (70.53)-(125.71) |       |
| 12.month                 | 98.19 ± 13.95| 99.31 | (77.55)-(119.05) | 0.629*|
| Body mass index          |             |        |             |       |
| 0.month                  | 15.44 ± 2.45| 15.36  | (10.88)-(20.14) |       |
| 12.month                 | 15.01 ± 1.78| 16.02  | (12.5)-(18.26) | 0.589*|
| Body mass index (SDS)    |             |        |             |       |
| 0. month                 | -0.99 ± 2.23| -0.45  | (-6.49)-(1.53) |       |
| 12. month                | -0.74 ± 1.83| 0.14   | (-3.79)-(1.48) | 0.638*|

Table IV. Seizure outcome and EEG findings in relation to antiepileptic drugs in patients receiving ketogenic diet.

|                          | ≤ 3 AED (n: 8 patients) | ≥ 4 AED (n: 10 patients) | P   |
|--------------------------|--------------------------|--------------------------|-----|
| Seizure control*         | a decrease of more than 50% | 5 (62.5%) | 5 (50%) | 0.664 |
|                         | a decrease of less than 50% | 3 (37.5%) | 5 (50%) |       |
| EEG findings*           | a decrease of more than 50% | 5 (62.5%) | 7 (70%) | 1.00  |
|                         | a decrease of less than 50% | 3 (37.5%) | 3 (30%) |       |

EEG: electroencephalogram
AED: antiepileptic drug
* A reduction of ≥50% in the number of seizures was accepted as a response to ketogenic diet.
*+ A reduction of more than 50% in epileptiform discharges in EEG was accepted as a response to ketogenic diet.
* Fischer exact test, p<0.05 is significant

Table III. The difference between anthropometric measurements of patients between baseline and 12th month of treatment.

|                          | Mean ± S.D. | Median | (Min)-(Max) | P     |
|--------------------------|-------------|--------|-------------|-------|
| Weight for age (kg)      |             |        |             |       |
| 0.month                  | 18.3 ± 7.45 | 16.85  | (7.2)-(34)  | 0.004*|
| 12.month                 | 20.85 ± 7.12| 21     | (8.8)-(31.5) |       |
| Weight for age (SDS)     |             |        |             |       |
| 0.month                  | -1.34 ± 3.19| -0.75  | (-11)-(2.97) |       |
| 12.month                 | -1.07 ± 2.32| -0.84  | (-6.61)-(3.53) | 0.816*|
| Height for age (cm)      |             |        |             |       |
| 0.month                  | 104.96 ± 21.05| 110.5 | (62)-(136)   |       |
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| 12.month                 | -1.12 ± 1.66| -1.25  | (-4.38)-(2.11) | 0.522*|
| Weight for height (%)    |             |        |             |       |
| 0.month                  | 97.59 ± 14.39| 96.93 | (70.53)-(125.71) |       |
| 12.month                 | 98.19 ± 13.95| 99.31 | (77.55)-(119.05) | 0.629*|
| Body mass index          |             |        |             |       |
| 0.month                  | 15.44 ± 2.45| 15.36  | (10.88)-(20.14) |       |
| 12.month                 | 15.01 ± 1.78| 16.02  | (12.5)-(18.26) | 0.589*|
| Body mass index (SDS)    |             |        |             |       |
| 0. month                 | -0.99 ± 2.23| -0.45  | (-6.49)-(1.53) |       |
| 12. month                | -0.74 ± 1.83| 0.14   | (-3.79)-(1.48) | 0.638*|

Table IV. Seizure outcome and EEG findings in relation to antiepileptic drugs in patients receiving ketogenic diet.

|                          | ≤ 3 AED (n: 8 patients) | ≥ 4 AED (n: 10 patients) | P   |
|--------------------------|--------------------------|--------------------------|-----|
| Seizure control*         | a decrease of more than 50% | 5 (62.5%) | 5 (50%) | 0.664 |
|                         | a decrease of less than 50% | 3 (37.5%) | 5 (50%) |       |
| EEG findings*           | a decrease of more than 50% | 5 (62.5%) | 7 (70%) | 1.00  |
|                         | a decrease of less than 50% | 3 (37.5%) | 3 (30%) |       |

EEG: electroencephalogram
AED: antiepileptic drug
* A reduction of ≥50% in the number of seizures was accepted as a response to ketogenic diet.
*+ A reduction of more than 50% in epileptiform discharges in EEG was accepted as a response to ketogenic diet.
* Fischer exact test, p<0.05 is significant
KD treatment; and nephrolithiasis was detected in the follow-up USG of four patients at the 12th month of the diet, though these values were not statistically significant (p = 0.308). Only one patient received topiramate therapy, according to our findings. In none of our patients did we keep a record of the urine calcium/creatinine ratio. There was no increase in the stone size of the patient who had nephrolithiasis at baseline. In the remaining two individuals, we attributed the kidney stone finding to KD.

At the end of the year-long treatment, total cholesterol (p = 0.014) and LDL-C (p = 0.019) levels were found to have increased significantly, while fasting blood glucose levels had decreased significantly when compared with the values at the beginning of the diet (p = 0.031). As for the other biochemical parameters, no statistically significant difference was noted between the findings before and after treatment. The biochemical parameter values of the patients at the beginning of the diet and in the 12th month are presented in Table VI.

### Discussion

The KD is a safe and effective approach to the treatment of DRE in children. Ketogenic diet directs the body’s metabolism to source energy from essential oils rather than glucose, although the mechanisms of action of KD related to seizure control remain unclear. Normally, the use of ketones in the brain is minimal. In patients receiving KD, ketone bodies cross the blood-brain barrier and are used as the energy source of the brain for the replacement of glucose. The main effects of the production of ketone bodies appear to be neurotransmitter modulation and antioxidant effects on the brain. The

### Table V. Side effects observed in patients during ketogenic diets and their distribution.

| Side effects     | Number (n) | Percentage (%) |
|------------------|------------|----------------|
| Constipation     | 10         | 55.6           |
| Halitosis        | 5          | 27.8           |
| Hypoglycemia     | 4          | 22.2           |
| Nephrolithiasis  | 4          | 28.5*          |
| Weight loss      | 2          | 11.1           |
| Metabolic acidosis| 1         | 5.6            |
| Diarrhea         | 1          | 5.6            |

*Data from 14 patients

### Table VI. Biochemical findings of the patients before the diet and at the 12th month of the diet.

| Biochemical parameters | Before the diet (0.month) | After the diet (12. month) | p* |
|------------------------|---------------------------|----------------------------|----|
|                        | Mean ± S.D.               | Min.-Max.                  | Mean ± S.D. | Min.-Max. |    |
| Fasting blood glucose (mg/dL) | 87.05 ± 18.78 | 69-151 | 74.37 ± 6.59 | 62-89 | 0.031* |
| Total cholesterol (mg/dL)      | 161.5 ± 5.99 | 82.6-97 | 190.75 ± 38.46 | 134-262 | 0.014* |
| LDL cholesterol (mg/dL)        | 91.90 ± 6.41 | 82.6-97 | 142.45 ± 31.37 | 100.8-176 | 0.019* |
| HDL cholesterol (mg/dL)        | 44.44 ± 12.39 | 22-62 | 41.12 ± 8.53 | 25-54 | 0.133 |
| Triglyceride (mg/dL)           | 123.33 ± 61.48 | 40-261 | 166.50 ± 119.92 | 65-454 | 0.205 |
| BUN (mg/dL)                   | 9.93 ± 4.59 | 1.7-22 | 8.50 ± 3.93 | 3-16 | 0.221 |
| Creatinine (mg/dL)            | 0.29 ± 0.091 | 0.13-0.49 | 0.26 ± 0.081 | 0.10-0.45 | 0.115 |
| ALT (U/L)                     | 6 ± 2.94 | 3-10 | 8.5 ± 5.80 | 3-14 | 0.071 |
| AST (U/L)                     | 23.35 ± 7.63 | 16-34 | 16.75 ± 3.5 | 13-21 | 0.11 |
| Albumin (g/dL)                | 4.12 ± 0.095 | 4.4-2.2 | 4.26 ± 0.47 | 3.64-4.80 | 0.996 |
| Hemoglobin (gr/dL)            | 11.93 ± 0.89 | 11.4-13.5 | 12.77 ± 1.61 | 10.8-17.10 | 0.71 |
| TSH (uIU/mL)                  | 4.53 ± 3.52 | 1.86-9.4 | 3.83 ± 1.65 | 1.9-5.78 | 0.911 |
| fT4 (ng/dL)                   | 1.47 ± 0.37 | 1.15-2.01 | 1.65 ± 0.25 | 1.42-1.91 | 0.490 |

*Paired samples t-test, SD: standard deviation, (Min)-(Max): minimum-maximum, mg/dL: milligram/deciliter, U/L: units per liter, gr/dL: gram/deciliter, uIU/mL: micro-international units/milliliter, ng/dL: nanogram/deciliter, LDL: low-density lipoprotein, HDL: high-density lipoprotein, BUN: blood urea nitrogen, ALT: alanine transaminase, AST: aspartate transaminase, TSH: thyroid stimulating hormone, fT4: free thyroxine
levels of inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and agmatine were found to be increased, whereas glutamate, the excitatory neurotransmitter, remained unchanged in rat hippocampus following exposure to ketogenic diet. The anticonvulsant effect of KD is also based on the inhibition of the rapamycin pathway. Ketogenic diet is the first treatment option for a number of metabolic diseases, such as glucose transporter type 1 deficiency syndrome (GLUT-1) and pyruvate dehydrogenase deficiency (PDHD), and it has also been shown to be effective in some epilepsy and genetic syndromes, such as myoclonic epilepsy, severe myoclonic epilepsy in infancy (Dravet syndrome), myoclonic-astatic epilepsy (Doose syndrome), West syndromes resistant to corticosteroids and other drugs, Lennox–Gastaut syndrome, Lafora disease, Rett syndrome and Landau-Kleffner syndrome.

Qiong et al. reported KD to be the most effective treatment for Doose syndrome (100%), and an impact rate of 57.9% was shown on West syndrome. In the present study, similar to the literature, four patients with West, Lennox-Gastaut and Rett syndromes, showed more than a 50% reduction in the rate of seizures after classical KD treatment.

There are four basic forms of KD therapy: classic KD (long-chain triglyceride), MAD, medium-chain triglyceride (MCT) diet and low-glycemic-index (LGI) diet.

In the present study, eight (57.1%) of the 14 patients given the classical KD and two (50%) of four patients who received MAD experienced a 50% decrease in the number of seizures. In the other patients, the duration of seizures reduced. In a Cochrane review of studies conducted between 1966 and 2003, at least 38% of the patients experienced a 50% reduction in seizures when compared to the controls in the third month of KD. Martin-McGill et al. reported seizure-free rates in classical KD patients to reach 55%, and the decrease in seizure rates to reach 85% after three months. Studies evaluating the effectiveness of MAD report seizure-free rates of up to 25% and seizure reduction rates of up to 60% in children. Caraballo et al. reporting the results of the KD treatment of 11 refractory myoclonic-astatic epilepsy patients, identified a seizure reduction of 75–99% in two, 50–74% in two, and 100% in two patients. Güzel et al. administered olive oil-based KD treatment to 389 patients, and in the third month of treatment, a 39.8% seizure-free rate and a 50% reduction in seizures (rate of 34.9%) was recorded. In the same study, 43.1% of 160 patients whose treatment was completed in the 12th month were completely seizure-free, and 40% had experienced a 50% reduction in seizures. In the first year of the diet, a decrease of more than 50% in seizures was found in 10 patients (55.6%), and this difference was statistically significant, while the seizure-free rate was 5.55% (n = 1). A meta-analysis showed no difference in the efficacy of classical KD and MAD in children and adolescents with intractable epilepsy. Poorshiri et al. found the efficacies of classical KD and MAD in the treatment of refractory epilepsy to not be significantly different, although MAD was reported to be more favorable in terms of tolerability and the fewer associated side effects.

Ketogenic diet can also significantly improve the EEG findings of children with epilepsy. In the present study, the initial EEG findings of three of the 18 DRE patients were normal, and two patients had electrical status epilepticus findings. The EEG findings of 10 patients showed a decrease of more than 50% in epileptiform discharges at the 12th month of treatment. In one patient, the seizures decreased by more than 50% in the first six months, but increased again afterwards. The initial EEG findings revealed that epileptic discharges originated from both hemispheres, while completely normal EEG findings were found after the sixth month. Hallböök et al. found that the frequency of interictal epileptic discharges decreased significantly after three months of KD treatment. Dresler et al. reported a significant improvement in the frequency of interictal epileptic discharge and background activity after six months of KD treatment. In another
study, the EEG results of 34 children with DRE were examined, and significant decreases were noted in the epileptic discharge index during sleep and clinical seizures after six months of KD treatment. In the same study, prolonging the duration of KD treatment significantly improved the patients’ background activity irregularities, and it was reported that some children may show improvement in motor function, language ability and cognitive function. When we evaluated according to the number of AED, the EEG findings of five patients using three or less AEDs (%62.5) and seven patients using four or more AEDs (%70) showed a decrease of more than 50% in epileptiform discharge. This result is not statistically significant, and further studies are needed in terms of baseline AED number and seizure responsiveness to KD treatment.

Growth may be negatively affected in children receiving KD due to energy and protein restriction. In Peterson et al. the height-for-age Z-scores significantly decreased in children who received KD for 12 months. In a study from Turkey, a decrease of approximately 7% was found in the body weight of children in the third month of KD treatment. Contrary to the literature, a statistically significant increase in body weight was found after one year of KD treatment in children in the present study. Weight loss was observed in only two patients (11.1%). One of the most serious adverse effects of the ketogenic diet is stagnation in height development, which cannot be prevented in long-term use due to its low protein content. Contrary to the literature, a statistically significant increase in body weight was found after one year of KD treatment in children in the present study. However, the yearly growth rates of all patients were analyzed according to their age groups. We found that the annual growth rate of our patients, especially those aged 5-72 months, who had a higher protein requirement, fell behind compared to their age [mean 4.1 cm (2-6 cm)]. The growth in height in four MAD patients was found to be appropriate for their age groups. Evidence suggests that alterations in the lipid profile, particularly an increase in TC and LDL-C values, may be evident in individuals receiving KD therapy. In the present study, total cholesterol and LDL-C levels increased significantly at the end of the one-year treatment when compared with those at baseline, and fasting blood glucose levels decreased significantly, although remaining within normal limits. There are many doubts about the negative impact of KD on TC, TGs, and lipoprotein concentrations. However, some studies suggest that extreme carbohydrate restriction, which is typical of KD, results in favorable changes in plasma lipid concentrations, with a reduction in TC, LDL-C, and TGs and a rise in HDL-C. Chronic elevations in blood LDL-C and TC concentrations may raise the risk of cardiovascular disease, particularly in adult patients on long-term KD treatment. Before the diagnosis of KD, persons with a higher cardiovascular risk should be screened to ensure that the patient understands the risks and advantages of dietary therapy.

Ketogenic diet causes thyroid dysfunction, and L-thyroxine treatment may be required, meaning that thyroid function should be monitored regularly in epileptic patients treated with KD. Finally, in the present study, KD had no significant effect on thyroid function, hematological parameters, liver function or kidney function. In the study by Güzel et al., the mean cholesterol, LDL-C and TG levels were significantly higher than at pretreatment levels in the first, third, sixth and 12th months of an olive-oil-based KD treatment. The mean BMI SDS and HDL-C levels did not differ significantly between baseline and follow up. After starting KD, patients should be followed up regularly for side effects. In our study, the most common side effect related to the diet was constipation, while other side effects were halitosis, hypoglycemia, weight loss, metabolic acidosis, diarrhea and nephrolithiasis. The most common side effects of the KD treatment for DRE are vomiting and constipation, while other side effects include diarrhea, dysphagia, drowsiness, lower respiratory tract infection.
Ketogenic diet therapy is a reliable treatment approach to the treatment of DRE in children, and can also play a favorable role in cognitive and motor functions in children. Our study findings suggest that KD treatment provides good clinical efficacy against DRE, and can significantly reduce the frequency of epileptic discharges on EEG. The small number of patients can be considered a major limitation of our study, and further research is needed to evaluate the long-term effects of KD. Finally, KD therapy should not be considered as the final option for patients whose seizures cannot be controlled with medication, but it should be started early, especially in patients with epileptic syndromes.

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Ethical approval

Ethical approval for the research was obtained from the Ethics Committee of Eskisehir Osmangazi University, Medical Faculty (Dated 12.05.2020, number: 25403353-050.99-E.51610, decision number: 18), and the study was conducted in accordance with the Declaration of Helsinki.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: GKY, MY; data collection: GKY, MY, AÇU; analysis and interpretation of results: HÖ; draft manuscript preparation: GKY, CY, KBÇ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Wilfong A. Seizures and epilepsy in children: classification, etiology, and clinical features. Available at: https://www.uptodate.com/contents/seizures-and-epilepsy-in-children-classification-etiology-and-clinical-features (Accessed on June 30, 2021).

2. Rezaei S, Abdurahman AA, Saghazadeh A, Badv RS, Mahmoudi M. Short-term and long-term efficacy of classical ketogenic diet and modified Atkins diet in children and adolescents with epilepsy: a systematic review and meta-analysis. Nutritional Neuroscience 2019; 22: 317-334. https://doi.org/10.1080/1028415X.2017.1387721

3. Wells J, Swaminathan A, Paseka J, Hanson C. Efficacy and safety of a ketogenic diet in children and adolescents with refractory epilepsy-a review. Nutrients 2020; 12: 1809-1828. https://doi.org/10.3390/nu12061809

4. Milczarek O, Jarocha D, Starowicz-Filip A, Kwiatkowski S, Badyra B, Majka M. Multiple autologous bone marrow-derived CD271+ mesenchymal stem cell transplantation overcomes drug-resistant epilepsy in children. Stem Cells Transl Med 2018; 7: 20-33. https://doi.org/10.1002/sctm.17-0041

5. Kwan P, Arzimanoglou A, Berg AT, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010; 51: 1069-1077. https://doi.org/10.1111/j.1528-1167.2009.02397.x
6. Barzegar M, Afghan M, Tarmahi V, Behtari M, Khameianh SR, Raeisi S. Ketogenic diet: overview, types, and possible anti-seizure mechanisms. Nutr Neurosci 2021; 24: 307-316. https://doi.org/10.1080/1028415X.2019.1627769
7. Wu Q, Wang H, Fan YY, et al. Ketogenic diet effects on 52 children with pharmacoresistant epileptic encephalopathy: A clinical prospective study. Brain Behav 2018; 8: e00973. https://doi.org/10.1002/brb3.973
8. Hallböök T, Sjölander A, Amark P, Miranda M, Bjurulf B, Dahlén M. Effectiveness of the ketogenic diet used to treat resistant childhood epilepsy in Scandinavia. Eur J Paediatr Neurol 2015; 19: 29-36. https://doi.org/10.1016/j.ejpn.2014.09.005
9. Suo C, Liao J, Lu X, et al. Efficacy and safety of the ketogenic diet in Chinese children. Seizure 2013; 22: 174-178. https://doi.org/10.1016/j.seizure.2012.11.014
10. Wilder RM. The effect of ketonemia on the course of epilepsy. Mayo Clin Bulletin 1921; 2: 302-308.
11. Thompson L, Fecské E, Salim M, Hall A. Use of the ketogenic diet in the neonatal the intensive care unit-safety and tolerability. Epilepsia 2017; 58: 36-39. https://doi.org/10.1111/epi.13650
12. Barborka CJ. Epilepsy in adults: results of treatment by ketogenic diet in one hundred cases. Arch Neuropsych 1930; 23: 904-914. https://doi.org/10.1001/archneurpsyc.1930.02220110066004
13. Nei M, Ngo L, Sirven JI, Sperling MR. Ketogenic diet in adolescents and adults with epilepsy. Seizure 2014; 23: 439-442. https://doi.org/10.1016/j.seizure.2014.02.015
14. Kossoff EH, Zupec-Kania BA, Auvin S, et al. Optimal clinical management of children receiving the ketogenic diet: updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open 2018; 3: 175-192. https://doi.org/10.1002/epi.22225
15. Van der Louw E, van den Hurk D, Neal E, et al. Ketogenic diet guidelines for infants with refractory epilepsy. Eur J Paediatr Neurol 2016; 20: 798-809. https://doi.org/10.1016/j.ejpn.2016.07.009
16. Calderón N, Betancourt L, Hernández L, Rada P. A ketogenic diet modifies glutamate, gammaaminobutyric acid and agmatine levels in the hippocampus of rats: a microdialysis study. Neurosci Lett 2017; 642: 158-162. https://doi.org/10.1016/j.neulet.2017.02.014
17. Gano LB, Patel M, Rho JM. Ketogenic diets, mitochondria, and neurological diseases. J Lipid Res 2014; 55: 2211-2228. https://doi.org/10.1194/jlr.R048975
18. Zhang Y, Wang Y, Zhou Y, Zhang L, Yu L, Zhou S. Therapeutic effects of the ketogenic diet in children with Lennox-Gastaut syndrome. Epilepsy Res 2016; 128: 176-180. https://doi.org/10.1016/j.eplepsyres.2016.11.003
19. Kelley SA, Kossoff EH. How effective is the ketogenic diet for electrical status epilepticus of sleep?. Epilepsy Res 2016; 127: 339-343. https://doi.org/10.1016/j.eplepsyres.2016.09.018
20. Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: Prospective single-center experience in 104 consecutive infants. Epilepsia 2010; 51: 1403-1407. https://doi.org/10.1111/j.1528-1167.2010.02586.x
21. Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. Cochrane Database Syst Rev 2018; 11: CD001903. https://doi.org/10.1002/14651858.CD001903.pub4
22. Levy RG, Cooper PN, Giri P. Ketogenic diet and other dietary treatments for epilepsy. Cochrane Database Syst Rev 2012; 3: CD001903. https://doi.org/10.1002/14651858.CD001903.pub2
23. Caraballo RH, Cersósimo RO, Sakr D, Cresta A, Escobar N, Fejerman N. Ketogenic diet in patients with myoclonic-astatic epilepsy. Epileptic Disord 2006; 8: 151-155. PMID: 16793577.
24. Güzel O, Uysal U, Arslan N. Efficacy and tolerability of olive oil-based ketogenic diet in children with drug-resistant epilepsy: a single center experience from Turkey. Eur J Paediatr Neurol 2019; 23: 143-151. https://doi.org/10.1016/j.ejpn.2018.11.007
25. Poorshiri B, Barzegar M, Tahmasebi S, Shiva S, Raeisi S, Ebadi Z. The efficacy comparison of classic ketogenic diet and modified Atkins diet in children with refractory epilepsy: a clinical trial. Acta Neurol Belg 2021; 121: 483-487. https://doi.org/10.1007/s13760-019-01225-0
26. Hallböök T, Köhler S, Rosén I, Lundgren J. Effects of ketogenic diet on epileptiform activity in children with therapy resistant epilepsy. Epilepsy Res 2007; 77: 134-140. https://doi.org/10.1016/j.eplepsyres.2007.09.008
27. Dressler A, Stöcklin B, Reithofer E, et al. Long- term outcome and tolerability of the ketogenic diet in drug- resistant childhood epilepsy- the Austrian experience. Seizure 2010; 19: 404-408. https://doi.org/10.1016/j.seizure.2010.06.006
28. Ebus SCM, Lambrechts DA, Herraets IJT, et al. Can an early 24-hour EEG predict the response to the ketogenic diet? A prospective study in 34 children and adults with refractory epilepsy treated with the ketogenic diet. Seizure 2014; 23: 468-474. https://doi.org/10.1016/j.seizure.2014.03.008

29. Brownlow ML, Jung SH, Moore RJ, Bechmann N, Jankord R. Nutritional ketosis affects metabolism and behavior in Sprague-Dawley rats in both control and chronic stress environments. Front Mol Neurosci 2017; 10: 129. https://doi.org/10.3389/fnmol.2017.00129

30. Peterson SJ, Tangney CC, Pimentel-Zablah EM, Hjelmgren B, Booth G, Berry-Kravis E. Changes in growth and seizure reduction in children in the ketogenic diet as a treatment for intractable epilepsy. J Am Diet Assoc 2005; 105: 718-725. https://doi.org/10.1016/j.jada.2005.02.009

31. Çetin B, Köksal G, Çelik F, Topçu M. Epilepsi hastası çocuklarda ketojenik diyetin epileptik nöbet sayısı üzerine etkisi. Beslenme ve Diyet Dergisi 2013; 41: 27-34.

32. Neves GS, Lunardi MS, Lin K, Rieger DK, Ribeiro LC, Moreira JD. Ketogenic diet, seizure control, and cardiometabolic risk in adult patients with pharmacoresistant epilepsy: a review. Nutr Rev 2021; 79: 931-944. https://doi.org/10.1093/nutrit/nuaa112

33. Kose E, Guzel O, Demir K, Arslan N. Changes of thyroid hormonal status in patients receiving ketogenic diet due to intractable epilepsy. J Pediatr Endocrinol Metab 2017; 30: 411-416. https://doi.org/10.1515/jpem-2016-0281

34. Güzel O, Yilmaz U, Uysal U, Arslan N. The effect of olive oil-based ketogenic diet on serum lipid levels in epileptic children. Neurol Sci 2016; 37: 465-470. https://doi.org/10.1007/s10072-015-2436-2