Original Article

Ketogenic diet and growth in Chinese infants with refractory epilepsy

Yongfang Liu MSc[1,2], Juan Wang MSc[3], Zhongmin Gao MSc[1,3], Lijuan Xu MSc[3], Lin Kong MSc[1]

[1]*Department of Nutrition, Children's Hospital of Chongqing Medical University, National Clinical Research Center for Child Health and Disorders, Ministry of Education Key Laboratory of Child Development and Disorders*
[2]*Chongqing Key Laboratory of Paediatrics, Chongqing Key Laboratory of Child Health and Nutrition*
[3]*Department of Neurology, Children's Hospital of Chongqing Medical University, Chongqing, China*

Background and Objectives: This study evaluated the impact of 12 months of ketogenic dietary treatment (KDT) on growth in Chinese infants with refractory epilepsy. **Methods and Study Design:** The KDT group included patients who were divided into groups A (age 6-12 months), B (12-24 months) and C (24-36 months). The normal group included infants aged approximately 6-12 months, 12-24 months and 24-36 months who were classified into groups A1, B1 and C1, respectively. Data on height, weight, aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), zinc, iron, calcium, magnesium, and haemoglobin (Hb) were extracted from the medical records. Then, we compared the impacts of 12 months of KDT on growth. **Results:** Forty-one patients were included in the KDT group, and 90 infants were included in the normal group. The overall prevalence of underweight (WAZ <-2 SD), stunting (HAZ <-2 SD), wasting (BAZ <-2 SD), and overweight/obesity (BAZ ≥2 SD) were relatively lower in the A and B groups. The prevalence of anaemia in group A was significantly higher than that in group A1. No significant differences were observed in the KDT groups with regard to HDL, LDL, AST, ALT, iron, calcium, magnesium, or zinc. A greater than 50% reduction in weekly seizure frequency was evident in 100% of group A, 78.6% of group B and 77.8% of group C. **Conclusions:** The results revealed that patients less than 2 years old who received KDT maintained appropriate growth at the 12-month follow-up.

Key Words: ketogenic dietary treatment, children, anaemia, haemoglobin, blood lipids

INTRODUCTION

In the majority of children with epilepsy, antiepileptic drugs (AEDs) result in seizure remission. However, 20-30% of children with epilepsy may suffer from refractory epilepsy, and the chance of them responding to medication decreases dramatically after the failure to respond to more than one drug.[1] For children with uncontrolled epilepsy, the treatment options are epilepsy surgery, vagal nerve stimulation and ketogenic dietary treatment (KDT). The ketogenic diet (KD), a high-fat, moderate-protein and low-carbohydrate diet, is a valuable nonpharmacological therapeutic option for children with refractory epilepsy.[2-4] Typically, one-third of patients will experience a greater than 90% reduction in seizure frequency.[5] The KDT generally lasts for 1-3 years. In recent years, researchers have been increasingly concerned about the potential effect of a KD on children's growth. Negative impacts on growth percentiles have not been found in previous six-month follow-up investigations.[6,7] Nevertheless, numerous long-term studies[8-10] on KDs have shown a decrease in height or weight among participants. For a long time, KDs were not recommended for use during infancy (younger than 2 years old) because that is such a crucial period in development and there is the perception of a high risk of nutritional inadequacies associated with KDs. Indeed, infants are vulnerable and have specific nutritional requirements. However, current research has shown that KDs are highly effective and well tolerated in infants with epilepsy.[11,12] However, in the early stages of KDT, many paediatric neuroscientists prescribed KDs for children after infancy because they were concerned about nutritional inadequacies during this crucial period in neurodevelopment. Most of the studies have reported that children receiving KDT are over 2 years old. Studies on the effects of long-term KDT on growth in infants and young children remain scarce. KDT requires constant nutritional monitoring over time both to ensure its effectiveness and to reduce the likelihood of short- and long-term adverse effects. This

Corresponding Author: Lin Kong, Department of Nutrition, Children's Hospital of Chongqing Medical University, 136 Zhongshan 2nd Road, Yuzhong District, Chongqing, 400014, China.
Tel: +86 23 63635084
Email: konglin2020@163.com
Manuscript received 23 November 2020. Initial review completed 01 December 2020. Revision accepted 25 January 2021.
doi: 10.6133/apjcn.202103_30(1).0014

remains a problem in the context of infancy, early childhood and long-term effects.

The purpose of this study was to identify whether KDT results in altered growth during infancy (before the age of 3 years) in individuals over 12 months of age with intractable epilepsy. A better understanding of the long-term effects on growth may guide improvements in the KDT protocol to optimize growth, nutrition, and health status in these younger children.

METHODS

Participants, inclusion, and exclusion

This study was designed as an observational study with 2 groups. Children in the KDT group who were diagnosed with refractory epilepsy were enrolled in a 12-month KDT plan from November 2017 to June 2019 in the neurology centre. According to age, these patients were divided into the A (age 6-12 months), B (12-24 months) and C (24-36 months) groups. In the normal group, infants randomly selected from the Department of Child Health Care who were aged 6-12 months, 12-24 months and 24-36 months were assigned to the A1, B1 and C1 groups, respectively. All participants in this study were selected from the Children's Hospital of Chongqing Medical University, Chongqing, China. The study design is shown in Figure 1. This study was approved by the Ethics Review Committee of the Children's Hospital of Chongqing Medical University (approval number: 2017-122), and informed consent was obtained from each child's parents or guardians.

The KDT group inclusion criteria were as follows: (1) infants who were born full term and aged 6-36 months; (2) children with refractory epilepsy who had seizures at least twice a week and took two or more anticonvulsants; (3) individuals who underwent KDT for at least 12 months; and (4) children with no severe organ failure or thyroid disorders. In the normal group, infants who were born full term and without any chronic infectious diseases and infants with an unconfirmed but suspected syndromal diagnosis (as established by the clinical geneticist) were included. Infants with a syndromal or chromosomal disorder with a known influence on physical growth were excluded.

Data collection

Clinical data, including age, sex, weight, height, aspartate transaminase (AST), alanine transaminase (ALT), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), zinc, iron, calcium, magnesium, and haemoglobin (Hb), were collected at baseline and 1, 3, 6 and 12 months after the initiation of KDT. According to the diagnostic criteria for anaemia in infants formulated by the World Health Organization (WHO) in 2001, infants aged 6-59 months with a Hb concentration <110 g/L were diagnosed with anaemia.

During the initiation of KD, tolerance (i.e., gastrointestinal disturbances and vomiting) was assessed on a daily basis. All patients were followed up at monthly visits, and during these visits, each patient underwent 1) measurements of fasting blood serum β-hydroxybutyrate (BOH) and assessments of seizure frequency; 2) assessments of compliance with the prescribed diet regimen and supplement use and 3) screening for possible adverse effects of the diet (gastrointestinal disturbances and vomiting).

To monitor the possible adverse effects of the diet on weight, children were weighed at each monthly visit. To rule out individual variations in the measurement process, all anthropometric measurements were performed by the same researchers who were from the neurology centre in the Children's Hospital of Chongqing Medical University (Chongqing, China). Anthropometric measurements of the infants and young children were performed after admission using the same electronic baby scale (RCS-20). All measurements were performed in duplicate. Weight was recorded to the nearest 0.01 kg with the infants and young children minimally clothed and barefoot. Length was marked to the nearest 0.01 cm. Anthropometric data were assessed as Z-scores in the form of height-for-age Z-scores (HAZ), weight-for-age Z-scores (WAZ) and body

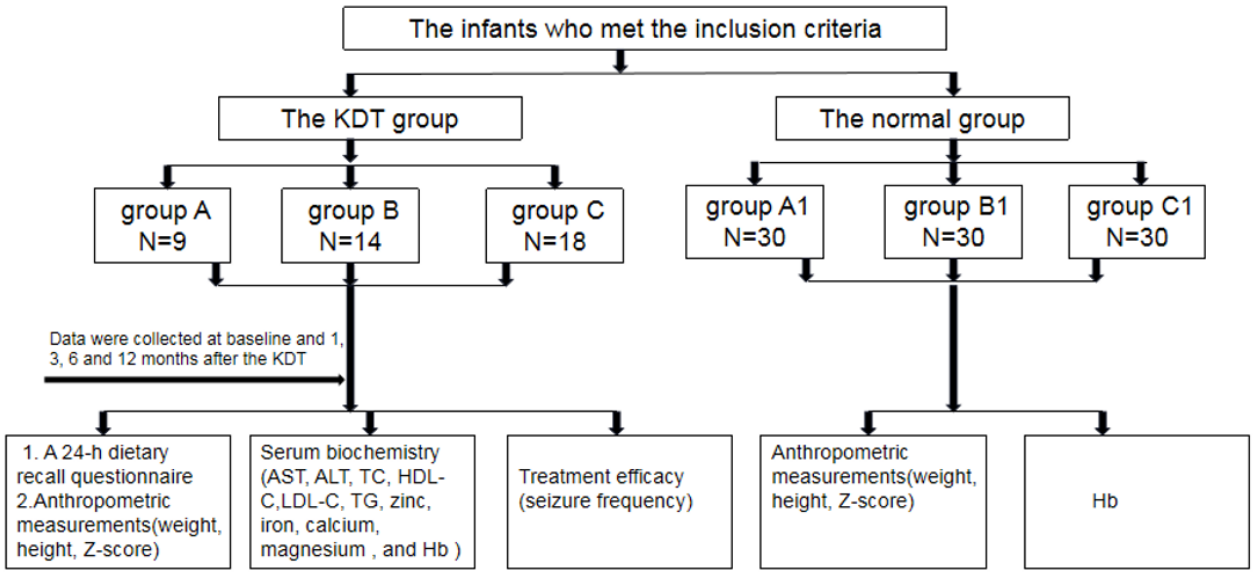

Figure 1. The study design. KDT: ketogenic dietary treatment; AST: aspartate transaminase; ALT: alanine transaminase; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TG: triglyceride; Hb: haemoglobin.

mass index (BMI)-for-age Z-scores (BAZ) based on the WHO Anthro 2005 (http://www.who.int/childgrowth/software/en/) and the U.S. National Center for Health Statistics data from 2006. A cut-off point of <-2 standard deviations (SDs) was defined as a low WAZ (underweight), low HAZ (stunting) and low BAZ (wasting); 2≤BAZ≤3 was defined as overweight, and BAZ >3 was defined as obesity.

KDT

KDT is a well-established and nonpharmacologic treatment used for children and adults with refractory epilepsy. There are currently 4 major therapies involving the classic KD: the modified Atkins diet (MAD), the medium-chain triglyceride diet (MCT) and the low-glycaemic index treatment (LGIT). The classic KD has been used continuously since 1921 and results in ketosis by limiting the intake of carbohydrates and protein to less than 10% of the total combined energy intake. In this study, the classic KD was the primary type of KD used in infants and young children. All participants were encouraged to initiate KDT while they were inpatients for at least one week. Furthermore, all children were recommended to use a commercial powdered formula (Qitong/Jiantong), which is intended for infants, during the diet initiation stage to achieve a stable blood ketone level before switching to more flexible self-prepared food. On a KD, the infant can continue to bottle feed. Formula may be given by bottle and/or tube. Based on individual tolerance and/or ketosis, a different ratio may be used (2:1-4:1) to achieve a blood serum BOH ≥2.0 mmol/L. A 24-h dietary recall questionnaire was used to assess dietary intake for all infants in the KDT group. The questionnaires were completed on the day of the monthly visit. Intakes were then calculated using the energy, protein, vitamin B1, vitamin B2, vitamin C, zinc, iron and calcium contents of the ingredients outlined in food composition tables (China Food Composition 2016). Due to the limited quantities of fruits, vegetables, enriched grains, and foods containing calcium that can be consumed while on a KDT, supplementation is essential, and the micronutrient supplements that were taken provided 50-100% of the Chinese Dietary Reference Intakes (DRIs, Chinese Nutrition Society, 2013, Science Press) (Table 1). The anticonvulsants were maintained unchanged for the first 6 months of the diet and were then adjusted according to the children's condition thereafter (Table 1).

Statistical analysis

Data were analysed with SAS software (version 8.1). $p<0.05$ was considered to indicate a significant difference. The Shapiro-Wilk test was used to investigate whether the concentrations of blood lipids, Hb, zinc, iron, calcium, and magnesium and the anthropometric indicators were normally distributed prior to analysis. The data are presented as the means±SDs or medians (M) (Q25, Q75) and the 95% confidence interval (CI). Paired t-tests were used to compare differences between the initial and final paired data with a normal distribution, while the paired Wilcoxon signed-rank test was used for nonnormally distributed data. Differences in prevalence were tested with chi-square tests.

RESULTS

Demographics

In the KDT group, forty-one children were enrolled, with 56% (n=23) boys and 44% (n=18) girls. There were 9 children in group A, 14 in group B, and 18 in group C. The average ages in group A, group B, and group C were 8.00±3.32 months, 16.6±3.05 months, and 29.8±4.93 months, respectively. In the normal group, the 30 infants in groups A1, B1 and C1 were randomly selected from the Department of Child Health Care. There was no difference in age, weight or height between the KDT group and the normal group. The prevalence of underweight, stunting and wasting in group C were significantly higher than those in group C1. Moreover, the prevalence of anaemia in group A was significantly higher than that in group A1 (Table 2). After 12 months of KDT, the prevalence of anaemia in group A decreased to 11.1%, while the prevalence of anaemia in group B and group C remained unchanged.

As shown in Table 3, in terms of energy intake, the children in groups A, B, and C consumed 578 (506-650) kcal/day, 731 (653-882) kcal/day, and 791 (688-924) kcal/day, respectively. The energy intake levels met the WHO recommendations for the age ranges in the study population 75-100% of the time. However, the dietary intakes of vitamin C, vitamin B2, and calcium were much lower than the Chinese recommended nutrient intake (RNI). Additionally, the intake of iron was significantly lower in the A group than in the B and C groups ($p<0.05$).

BAZ distribution

There was a rapid reduction in the BMI Z-score in the

Table 1. Drug use and micronutrient supplementation in the three groups of children treated with KDT

Drugs/Micronutrient	Group A (n=9)	Group B (n=14)	Group C (n=18)
Drugs†	4 (3-4)	4 (3-5)	4 (3-5)
Vitamin D (IU/d)	400	600	600
Calcium (mg/d)	200	500	500
Vitamin B-1 (mg/d)	0.25	0.5	0.5
Vitamin B-2 (mg/d)	0.3	0.3	0.3
Vitamin B-12 (μgd)	0.45	0.45	0.45
Vitamin C (mg/d)	30	30	30

KDT: ketogenic dietary treatment.

Drugs: Kipran, Depakine, Topiramate, Nitrazepam, lamotrigine, Methylprednisolone, Captopril, Clonazepam, Zonisamide, Immunoglobulin.

†Values are medians (range in 25th and 75th quartiles).

Table 2. Baseline characteristics of the children

GRP	N	Age (m)	Weight (kg)	Height (cm)	BAZ	WAZ	HAZ	Underweight (%)	Stunting (%)	Wasting (%)	Overweight /obesity (%)	Hb (g/L)	Anaemia (%)
A	9	8.00±3.32	8.20±1.62	67.0±4.90	0.74±2.35	0.03±1.73	-0.96±1.53	11.1%	33.3%	22.2%	33.3%	111±8	44.4%
A1	30	8.49±2.98	8.54±1.06	69.4±3.08	0.77±1.23	0.07±0.96	-0.62±1.17	3.33%	13.3%	6.67%	10%	119±9	6.67%
P	-	0.66	0.45	0.08	0.65	0.85	0.48	0.36	0.14	0.19	0.10	0.0001	0.01
B	14	16.6±3.05	10.5±2.05	78.3±5.37	0.56±2.15	0.06±1.52	-0.64±2.07	14.3%	14.3%	14.3%	7.14%	119±11	14.3%
B1	30	16.0±1.78	11.2±1.39	79.0±3.40	1.17±1.53	0.73±1.00	-0.24±0.95	0	3.33%	0	23.3%	122±9	10%
P	-	0.47	0.19	0.66	0.43	0.08	0.5	0.09	0.21	0.09	0.16	0.46	0.34
C	18	29.8±4.93	12.1±2.58	86.6±6.30	-0.08±2.15	-0.78±1.41	-1.34±1.52	22.2%	22.2%	22.2%	16.7%	125±10	11.1%
C1	30	28.4±4.25	12.9±4.25	89.6±5.07	0.22±1.04	0.07±0.82	-0.15±1.31	0	3.33%	0	3.33%	124±11	10%
P	-	0.32	0.24	0.07	0.81	0.02	0.006	0.02	0.05	0.02	0.12	0.80	0.36

GRP: group; BAZ: BMI-for-age Z-score; WAZ: weight-for-age Z-score; HAZ: height-for-age Z-score; Hb: haemoglobin.

Table 3. Daily consumption of major nutrients in the KDT group

Characteristic	Group A (n=9)	Group B (n=14)	Group C (n=18)
Energy (kcal)	578 (506-650)	731 (653-882)	791 (688-924)
Energy (% Chinese RNI)	77%-99%	78%-105%	76%-102%
Protein (g)	23.8 (20.8-32.0)	26.4 (22-31.2)	33.5 (26.0-34.0)
Protein (% Chinese RNI)	104%-160%	88%-125%	104%-136%
Vitamin C (mg RE)	17 (11-21.4)	25.8 (17-31.6)	26.1 (17-29.6)
Vitamin C (% Chinese RNI)	28%-54%	43%-79%	43%-74%
Vitamin B-1 (mg)	0.3 (0-0.34)	0.25 (0.1-0.7)	0.3 (0.1-0.7)
Vitamin B-1 (% Chinese RNI)	0-113%	17%-116%	17%-116%
Vitamin B-2 (mg)	0.2 (0-0.30)	0.15 (0-0.31)	0.31 (0-0.4)
Vitamin B-2 (% Chinese RNI)	0-60%	0-52%	0-67%
Zine (mg)	3.6 (2.7-3.7)	4 (2.7-4.8)	4 (3.1-4.6)
Zine (% Chinese RNI)	77%-106%	68%-120%	78%-115%
Iron (mg)	6.6 (5.6-7.8)	11.6 (7.2-13.6)	8.6 (7.2-12.9)
Iron (% Chinese RNI)	56%-78%	80%-151%	80%-143%
Calcium (mg)	115 (114-143)	205 (115-317)	224 (135-356)
Calcium (% Chinese RNI)	46%-57%	19%-53%	23%-61%

KDT: ketogenic dietary treatment; RNI: recommended nutrient intake.
Values are medians (range in 25th and 75th quartiles).

first 3 months after the initiation of KDT. Children in group A and group C had BMI Z-scores that were lower than those before the initiation of KDT (median Z-score 0.11 & 1.42, p=0.02; -0.48 &0.2, p=0.03). Over the course of 12 months on a KD, the BMI values in the three groups of children gradually increased from the initially low values, as shown in Table 4.

The overall prevalence of underweight, stunting, wasting, and overweight/obesity in groups A, B, and C at baseline were 11.1%, 14.3% and 22.2%; 33.3%, 14.3%, and 22.2%; 22.2%, 7.1%, and 22.2%; and 33.3%, 7.1%, and 16.7%, respectively. Over the course of 12 months of KDT, the overall prevalence of underweight, stunting, wasting, and overweight/obesity in children in groups A and B decreased. The prevalence of underweight and stunting in group C increased by 5.6% and 11.1%, respectively. However, those changes were not statistically significant (p>0.05). In addition, the prevalence of overweight/obesity in the three groups of children decreased significantly, and the prevalence of overweight/obesity among the three groups of children decreased to 0%, 0% and 5.6%, respectively.

Serum biochemistry

As shown in Table 5, after 12 months of KDT, the concentration of iron increased significantly in group A. No significant changes were shown in the KDT group with regard to HDL, LDL, AST, ALT, iron, calcium, magnesium, or zinc (p>0.05). However, the serum TC significantly decreased, while the serum TG significantly increased over the course of the study. No obvious abnormal liver function was found among children in the KDT group.

Treatment efficacy

The serum BOH levels in group A, group B, and group C were 3.3 (2.8-4.1) mmol/L, 3.5 (2.6-4.3) mmol/L, and 3.0 (2.8-4.4) mmol/L, respectively. There were no significant differences in serum BOH among the KDT groups. As shown in Table 6, 82.9% (34/41) of the children achieved a greater than 50% reduction in seizure frequency per week after 1 month of KDT, and 17.1% (7/41) of the children achieved a greater than 99% reduction in seizure frequency per week. Additionally, 3, 6, and 12 months after starting the diet, 68.3%, 78.0%, and 82.3% of the children, respectively, achieved a greater than 50% reduction in seizure frequency per week, while 17.1%, 19.5%, and 22.0% of the children, respectively, achieved a greater than 99% reduction in seizure frequency per week. Three of the children became seizure free at the end of the first month and remained seizure free throughout the study follow-up period. After 3 and 6 months of KDT, another 4 children (9.7%) became seizure free. After 1, 3, 6 and 12 months of KDT, 11.1% (1/9), 22.2% (2/9), 22.2% (2/9), and 33.3% (3/9) of the children in group A, respectively, had achieved a greater than 99% reduction in seizure frequency per week. The corresponding proportions of the children in group B were 21.4% (3/14), 7.1% (1/14), 7.1% (1/14) and 7.1% (1/14), respectively. The corresponding proportions of the children in group C were 16.7% (3/18), 22.2% (4/18), 27.8% (5/18), and 27.8% (5/18). Furthermore, after 12 months of KDT, a greater than 50% reduction in the weekly seizure frequency was evident in 100% of the children in group A, 78.6% of the children in group B and 77.8% of the children in group C, but the differences among the groups were not statistically significant.

DISCUSSION

KDT is a well-established, nonpharmacologic treatment used for children and adults with medication-refractory epilepsy. In this study, while undergoing KDT, none of the subjects exhibited hypoglycaemia (blood sugar <2.2 mmol/L) or high levels of ketosis. The patients had 1-4 daily stools, and there was no obvious diarrhoea, constipation or abdominal distension. A 24-h dietary recall questionnaire showed that the energy intake levels ranged from 75-100% of the WHO recommendations for the age ranges in the study population. The dietary intake levels

Table 4. Daily consumption of major nutrients in the KDT group

GRP	Mean	SD	95% CI for the estimate of the mean	Lower quartile	Median	Upper quartile	p value
A							
Baseline	0.74	2.31	-1.03-2.52	-0.67	1.42	2.58	
1st month	0.47	1.91	-0.99-1.95	-0.32	0.78	1.75	0.25
3rd month	0.33	1.68	-1.72-0.86	-1.05	0.11	0.59	0.02
6th month	0.48	1.61	-1.54-0.93	-0.60	0.32	0.22	0.11
12th month	0.67	1.12	-0.79-0.94	-0.16	0.46	0.11	0.36
B							
Baseline	0.62	2.38	-0.75-2.00	-0.50	0.67	1.93	
1st month	0.40	1.81	-0.64-1.44	-1.15	0.50	1.70	0.48
3rd month	0.38	1.47	-0.47-1.23	-0.80	0.42	1.51	0.78
6th month	0.46	1.31	-0.40-1.11	-0.56	0.72	1.15	0.85
12th month	0.57	0.95	-0.08-1.02	-0.08	0.75	1.15	0.92
C							
Baseline	0.09	2.36	-1.09-1.26	-1.54	0.2	1.80	
1st month	-0.51	2.14	-1.57-0.55	-2.21	-0.61	1.12	0.007
3rd month	-0.67	2.12	-1.72-0.39	-2.45	-0.48	0.74	0.03
6th month	-0.52	2.01	-1.52-0.48	-1.97	-0.07	0.48	0.11
12th month	-0.18	1.76	-1.06-0.69	-1.45	0.14	0.55	0.45

KDT: ketogenic dietary treatment; GRP: group; SD: standard deviation.

Table 5. Effects of a KD on serum biochemistry

GRP	TC	TGs	HDL	LDL	AST	ALT	Ca	Mg	Fe	Zn
A										
Baseline	4.60±1.78	1.26±0.62	1.45±0.39	2.75±1.76	29.0±7.85	26.4±14.1	2.42±0.72	0.86±0.11	15.7±6.47	13.6±1.97
12th month	1.61±0.94	3.77±0.56	0.92±0.34	1.94±0.47	24.1±6.44	17.4±7.08	2.48±0.18	0.93±0.06	18.1±5.51	12.7±2.3
Change	-2.97	2.4	-0.35	-1.5	-5.5	-9.99	0.05	0.09	2.88	-0.40
95% CI	-5.31--0.62	1.82-2.98	-0.85-0.15	-4.27-1.26	-11.2-0.17	-24.2-4.27	-0.22-0.31	-0.01-0.18	1.07-4.68	-2.50-1.70
p	0.02	0.0003	0.12	0.2	0.06	0.14	0.68	0.08	0.007	0.67
B										
Baseline	4.15±0.82	1.50±0.54	1.05±0.24	2.69±0.71	34.3±13.2	23.9±12.4	2.50±0.17	0.93±0.10	21.0±10.7	11.8±2.12
12th month	2.36±0.54	3.56±0.25	0.88±0.11	1.94±0.21	33.4±9.81	20.8±13.9	2.41±0.13	0.89±0.05	20.2±7.18	14.2±3.84
Change	-1.41	2.05	-0.06	-0.32	-3.66	-3.03	-0.11	-0.03	-0.85	2.38
95% CI	-2.03--0.79	0.91-3.18	-0.18-0.07	-0.73-0.09	-13.4-6.10	-16.5-10.5	-0.27-0.05	-0.12-0.06	-4.76-3.11	-0.57-5.22
p	0.0002	0.01	0.25	0.08	0.73	0.71	0.06	0.26	0.47	0.09
C										
Baseline	3.96±1.03	1.44±1.07	1.19±0.37	2.32±0.75	34.9±11.1	22.0±16.2	2.38±0.16	0.96±0.20	29.6±17.5	12.6±3.06
12th month	2.77±0.66	3.91±0.44	1.13±0.55	1.96±0.65	39.9±16.0	25.3±11.7	2.14±0.60	0.87±0.06	28.0±11.1	12.9±2.78
Change	-1.44	2.43	-0.11	-0.86	3.65	3.69	-0.26	-0.12	-1.48	0.48
95% CI	-2.15--0.74	0.79-4.06	-0.81-0.60	-1.85-0.13	-4.84-12.2	-16.6-23.9	-0.67-0.15	-0.28-0.04	-4.99-2.03	-0.64-1.59
p	0.0008	0.01	0.72	0.08	0.88	0.95	0.24	0.17	0.47	0.43

KD: ketogenic diet; GRP: group; TC: total cholesterol; TGs: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST: aspartate transaminase; ALT: alanine transaminase.

Table 6. Retention rate and seizure outcomes 1, 3, 6 and 12 months after the initiation of KDT (n=41)

Seizure frequency per week	At the end of the 1st month				At the end of the 3rd month				At the end of the 6th month				At the end of the 12th month			
	A	B	C	Total	A	B	C	Total	A	B	C	Total	A	B	C	Total
90-99% reduction in seizures	1	3	3	7	2	1	4	7	2	1	5	8	3	1	5	9
50-90% reduction in seizures	5	10	12	27	5	8	8	21	6	9	9	24	6	10	9	25
<50% reduction in seizures	3	1	3	7	2	5	6	13	1	4	4	9	0	3	4	7

of vitamin C, vitamin B-2, and calcium were much lower than the Chinese RNI values. However, the 24-h dietary recall questionnaire also showed that the intake of iron was significantly lower in group A than in groups B and C. The mean concentration of Hb in group A was significantly lower than that in group A1, and the prevalence of anaemia in group A was significantly higher than that in group A1. It is suggested that 6- to 12-month-old children undergoing KDT should take iron supplements.

Neurologists are particularly concerned about the long-term health risks of KDs, especially those related to growth. There is evidence that children on a KD have impaired growth,[13,14] and younger children may be at a relatively greater risk.[15] Long-term follow-up of children treated with a KD in the past has suggested that although growth does improve after the KD is discontinued, height gain remains below the expected level.[16] In this study, malnutrition was relatively common in infants and young children with refractory epilepsy. We sought to investigate the linear trend in growth in children who were treated with a KD for 12 months. The BAZ decreased rapidly in the first 3 months. In addition, the prevalence of overweight/obesity decreased significantly. After 3 months, both the weight and BAZ began to show upward trends. By 12 months, the proportion of children in the standard weight range increased significantly compared to that before KDT. The results showed that patients younger than 2 years of age maintained appropriate growth at the 12-month follow-up. The energy requirements of infants with epilepsy may vary substantially. There is no consensus in the literature on how to calculate energy requirements in infants younger than 6 months old. Often, a percentage (75-100%) of the recommended daily allowance (RDA) of energy is used.[17] For infants, the energy requirements must be based on the intake recorded in the food diary, and recent growth must be considered when the intake is compared with the RDA for age and sex. It is necessary to provide additional energy if the growth curve declines or the patient fails to thrive. Using the ideal weight/age or weight/height should be considered to ensure catch-up growth.

A KD is a special diet characterized by high fat, moderate protein and restricted carbohydrate levels, and long-term high-fat intake will affect blood lipids. It was reported that 14-59% of the children had elevated serum TC and TG levels; these levels in 60% of the participants gradually recovered and remained normal after 12 months.[18,19] In this study, after 12 months of KDT, no statistically significant changes were shown in the levels of HDL, LDL, AST, ALT, iron, calcium, magnesium, or zinc in children in the KDT group. Furthermore, no obviously abnormal liver function was observed in children in the KDT group. While the serum TG levels significantly increased over the course of the study, the blood TG levels of children undergoing KDT significantly increased, possibly due to the high intake of saturated fatty acids. Furthermore, dyslipidaemia can be observed during classic KDT. Strategies to prevent KD-induced hyperlipidaemia include increasing the consumption of MCT and olive oil; supplementing with omega-3 fatty acids or carnitine; decreasing the intake of trans fat, saturated fat, and cholesterol; decreasing the KD ratio; and excluding all fatty meats, egg yolks, cream, butter, animal fat, palm oil and coconut oil.[20,21]

KDT can effectively treat epilepsy in individuals from infancy through adulthood.[22] For years, it was thought that infants had difficulty maintaining ketosis while meeting their growth requirements. As a result, a KD was not recommended for children younger than 2 years of age. A recent case report showed that a KD was safe and effective for six-week-old infants.[23] In fact, there is now preliminary evidence that children younger than 2 years old may be an ideal population for treatment with a KD.[24,25] This study also found that among the 41 infants aged 0-3 years who were on the classic KD, the frequency of seizures per week decreased by more than 50% after 12 months, and the proportion of infants younger than 1 year old who achieved a greater than 50% decrease in seizure frequency tended to be greater than the proportion of 1- to 2-year-old children and 2- to 3-year-old children (100%, 78.6%, and 77.8%, respectively). Moreover, the proportion of infants younger than 1 year old who achieved a greater than 90% reduction in seizure frequency was higher than those of infants in Group B and Group C after 12 months (33.3%, 17.1%, and 27.8%, respectively). These findings suggest that initiating KDT in children with refractory epilepsy at a younger age may be more beneficial.

Conclusion

As shown in Figure 2, this study indicated that KDT was effective, safe, and well tolerated in infants and young children with refractory seizures. After 12 months of KDT, the prevalence of anaemia and malnutrition decreased in children with refractory seizures .The Patients in the KDT group who were younger than 2 years old maintained appropriate growth at the 12-month follow-up. Furthermore, it also showed that children younger than 1 year old may be an ideal population for KDT. The results of this study should be interpreted in light of certain limitations. This was a nonblinded, single-centre, open-label trial. In addition, because of the small sample size, we could not assess the relationship between seizure type and the response to the diet.

AUTHOR DISCLOSURES

The authors declare that there are no conflicts of interest regarding the publication of this paper.

REFERENCES

1. Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. J Child Neurol. 2009;24:979-88. doi: 10.1177/0883073809337162..
2. Kinsman SL, Vining EP, Quaskey SA, Mellits D, Freeman JM. Efficacy of the ketogenic diet for intractable seizure disorders: review of 58 cases. Epilepsia. 1992;33:1132-6. doi: 10.1111/j.1528-1157.1992.tb01770.x.
3. Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. Pediatrics. 1998;102:1358-63. doi: 10.1542/peds.102.6.1358.
4. Freeman JM, Kossoff EH, Hartman AL. The ketogenic diet: one decade later. Pediatrics. 2007;119:535-43. doi: 10.1542/peds.2006-2447.

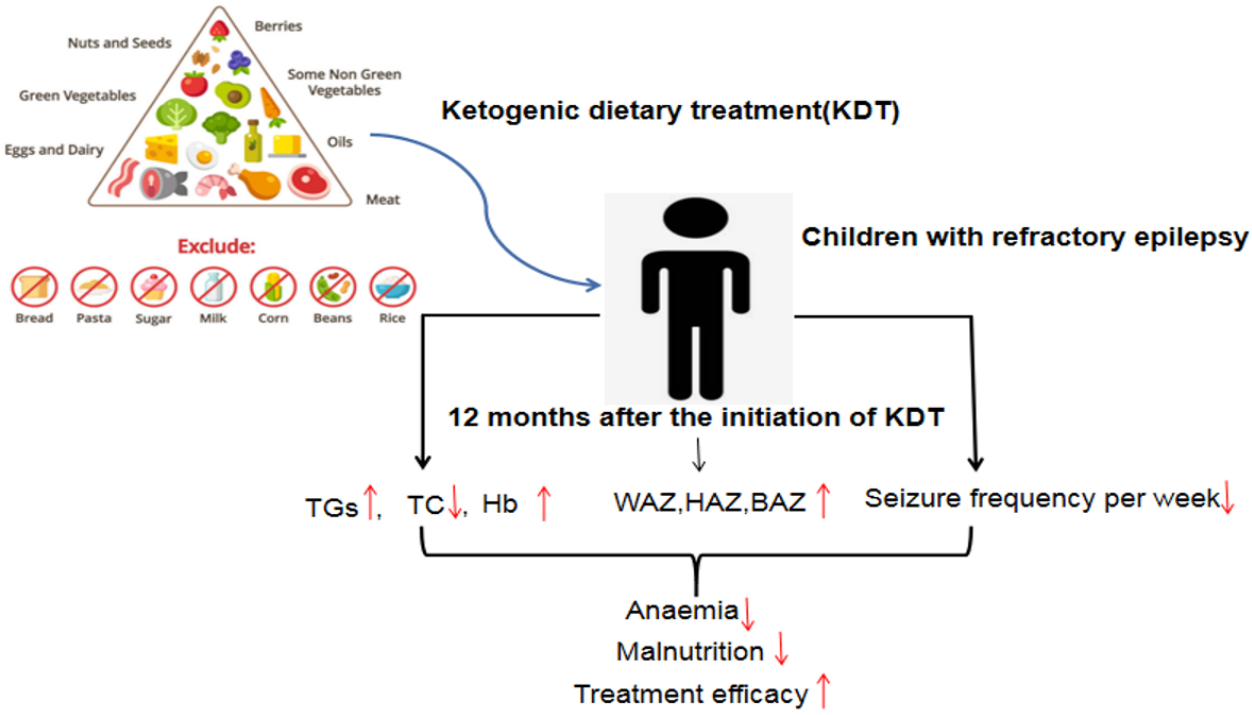

Figure 2. Effects of the ketogenic diet on malnutrition and anaemia in these children with refractory epilepsy. TGs: triglycerides; TC: total cholesterol; Hb: haemoglobin; WAZ: weight-for-age Z-score; HAZ: height-for-age Z-score; BAZ: BMI-for-age Z-score.

5. Henderson CB, Filloux FM, Alder SC, Lyon JL, Caplin DA. Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. J Child Neurol. 2006;21:193-8. doi: 10.2310/7010.2006.00044.
6. Couch SC, Schwarzman F, Carroll J, Koenigsberger D, Nordli DR, Deckelbaum RJ, DeFelice AR. Growth and nutritional outcomes of children treated with the ketogenic diet. J Am Diet Assoc. 1999;99:1573-5. doi: 10.1016/S0002-8223(99)00387-9.
7. Ferraris C, Guglielmetti M, Pasca L, De Giorgis V, Ferraro OE, Brambilla I et al. Impact of the ketogenic diet on linear growth in children: a single-center retrospective analysis of 34 cases. Nutrients. 2019;11:1442. doi: 10.3390/nu11071442.
8. Liu YM, Williams S, Basualdo-Hammond C, Stephens D, Curtis R. A prospective study: growth and nutritional status of children treated with the ketogenic diet. J Am Diet Assoc. 2003;103:707-12. doi: 10.1053/jada.2003.50136.
9. Williams S, Basualdo-Hammond C, Curtis R, Schuller R. Growth retardation in children with epilepsy on the ketogenic diet: a retrospective chart review. J Am Diet Assoc. 2002;102:405-7. doi: 10.1016/s0002-8223(02)90093-3.
10. Peterson SJ, Tangney CC, Pimentel-Zablah EM, Hjelmgren B, Booth G, Berry-Kravis E. Changes in growth and seizure reduction in children on the ketogenic diet as a treatment for intractable epilepsy. J Am Diet Assoc. 2005;105:718-25. doi: 10.1016/j.jada.2005.02.009.
11. Rubenstein JE. Use of the ketogenic diet in neonates and infants. Epilepsia. 2008;49(Suppl 8):30-2. doi: 10.1111/j.1528-1167.2008.01829.x.
12. 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;51:1403-7. doi: 10.1111/j.1528-1167.2010.02586.x.
13. Groesbeck DK, Bluml RM, Kossoff EH. Long-term use of the ketogenic diet in the treatment of epilepsy. Dev Med Child Neurol. 2006;48:978-81. doi: 10.1017/s0012162206002088.
14. Groleau V, Schall JI, Stallings VA, Bergqvist CA. Long-term impact of the ketogenic diet on growth and resting energy expenditure in children with intractable epilepsy. Dev Med Child Neurol. 2014;56:898-904. doi: 10.1111/dmcn.12462.
15. Vining EP, Pyzik P, McGrogan J, Hladky H, Anand A, Kriegler S, Freeman JM. Growth of children on the ketogenic diet. Dev Med Child Neurol. 2002;44:796-802. doi: 10.1017/s0012162201002961.
16. Patel A, Pyzik PL, Turner Z, Rubenstein JE, Kossoff EH. Long-term outcomes of children treated with the ketogenic diet in the past. Epilepsia. 2010;51:1277-82.doi: 10.1111/j.1528-1167.2009.02488.x.
17. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R et al. Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3:175-92. doi: 10.1002/epi4.12225.
18. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004;45:1116-23. doi: 10.1111/j.0013-9580.2004.10004.x.
19. Kwiterovich PO Jr, Vining EP, Pyzik P, Skolasky R Jr, Freeman JM. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA. 2003;290:912-20. doi: 10.1001/jama.290.7.912.
20. Nizamuddin J, Turner Z, Rubenstein JE, Pyzik PL, Kossoff EH. Management and risk factors for dyslipidemia with the ketogenic diet. J Child Neurol. 2008;23:758-61. doi: 10.1177/0883073808318061.
21. Güzel O, Yılmaz U, Uysal U, Arslan N. The effect of olive oil-based ketogenic diet on serum lipid levels in epileptic children. Neurol Sci. 2016;37:465-70. doi: 10.1007/s10072-015-2436-2.
22. Ye F, Li XJ, Jiang WL, Sun HB, Liu J. Efficacy of and patient compliance with a ketogenic diet in adults with intractable epilepsy: a meta-analysis. J Clin Neurol. 2015;11:26-31. doi: 10.3988/jcn.2015.11.1.26.

23. Thompson L, Fecske E, Salim M, Hall A. Use of the ketogenic diet in the neonatal intensive care unit-Safety and tolerability. Epilepsia. 2017;58:e36-e39. doi: 10.1111/epi.13650.
24. Kim JA, Yoon JR, Lee EJ, Lee JS, Kim JT, Kim HD, Kang HC. Efficacy of the classic ketogenic and the modified Atkins diets in refractory childhood epilepsy. Epilepsia. 2016;57:51-8. doi: 10.1111/epi.13256.
25. Dressler A, Trimmel-Schwahofer P, Reithofer E, Gröppel G, Mühlebner A, Samueli S, Grabner V, Abraham K, Benninger F, Feucht M. The ketogenic diet in infants--Advantages of early use. Epilepsy Res. 2015;116:53-8. doi: 10.1016/j.eplepsyres.2015.06.015.