Safety and tolerability of the ketogenic diet used for the treatment of refractory childhood epilepsy: a systematic review of published prospective studies

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Review article

Background: **To review the available evidence from prospective studies on the safety and tolerability of the ketogenic diet (KD) for the treatment of refractory childhood epilepsy.**

Methods: **A comprehensive bibliographic search was performed with the aim of retrieving prospective studies that monitored adverse effects (AEs) in children after receiving the classic or medium-chain triglyceride KD therapy for refractory epilepsy.**

Results: **A total of 45 studies were retrieved, including 7 randomized controlled trials. More than 40 categories of AEs were reported. The most common AEs included gastrointestinal disturbances (40.6%), hyperlipidemia (12.8%), hyperuricemia (4.4%), lethargy (4.1%), infectious diseases (3.8%) and hypoproteinemia (3.8%). Severe AEs, such as respiratory failure and pancreatitis, occurred in no more than 0.5% of children. Specifically, patients receiving KD therapy should be monitored for osteopenia, urological stones, right ventricular diastolic dysfunction, and growth disturbance. The total retention rates of the diet for 1 year and 2 years were 45.7% and 29.2%, respectively. Nearly half of the patients discontinued the diet because of lack of efficacy. AEs were not the main reason for the KD discontinuation. None of the 24 deaths reported after initiation of the diet was attributed to the KD.**

Conclusions: **KD is a relatively safe dietary therapy. However, because the KD can cause various AEs, it should be implemented under careful medical supervision. Continuous follow-up is needed to address the long-term impact of the diet on the overall health of children.**

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Introduction

Epilepsy has remained a challenging neurological disorder for centuries. Despite the successful approval of a number of new antiepileptic drugs in the past 20 years, 25%-30% of patients with epilepsy are still intractable.[1] The ketogenic diet (KD), first introduced by Wilder at the Mayo Clinic in 1921, seeks to mimic the effect of starvation by using a high fat, adequate-protein, and low-carbohydrate diet with restricted calories, to generate ketone bodies (acetoacetate, acetone and beta-hydroxybutyrate).[2,3] It needs to be carefully calculated to be nutritionally adequate for each individual. The classical KD provides 90% of calories from long-chain fat, a minimum of 1 g/kg of protein, and minimal carbohydrates, with a ratio of fat to protein and carbohydrates by weight (ketogenic ratio) at 2 to 4:1.[2,4] Over the last one to two decades, this diet has regained popularity for treatment of medically refractory epilepsy. The reported efficacy of KD (>50% reduction in seizures) is 20.4%-56% for intractable childhood epilepsy.[3-5] The antiepileptic mechanism of the KD has been elusive. It seems that multiple mechanisms, including the production of ketone bodies, the decrease of glucose and reactive oxygen species, the increase in adenosine triphosphate, creatinine and gamma-aminobutyric acid levels after consuming the diet, contribute to the anticonvulsive effect of the KD.[6]

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As a special formula diet, the KD provide daily nutrition needs for children, meanwhile controls seizure and decreases the use of antiepileptic drugs; therefore, children actually benefit a lot from this dietary therapy. However, KD therapy is not as safe as the ordinary diet and can cause a series of adverse effects (AEs). Consisting of 70%-90% of energy from fat, the KD can cause hyperlipidemia, leading to concerns about the increased risk of atherosclerosis with the use of this diet.[7] With restricted calorie and limited protein in the dietary regimen, the KD might also result in decelerated height velocity and growth failure.[8,9] Moreover, kidney stones have been reported in children who initiate the diet.[10]

With the increasing use of the KD to treat children with pharmacoresistant epilepsy, it is important to understand its full impact on the child's well being. The objective of this study was to systematically review the existing evidence from prospective studies about the safety and tolerability of the KD in the treatment of children with refractory epilepsy.

Methods

Literature search

A bibliographic search was performed using PubMed (1966-December 2015), MEDLINE database (OVID, 1946-December 2015), EMBASE database (1966-December 2015), Chinese Biomedical Literature Database (CBM) (1978-December 2015), Chinese Academic Journal Network Publishing Database (1915-December 2015), and Chinese Science & Technology Journal Database (1989-December 2015) with the aim of retrieving prospective studies that monitored AEs in children receiving KD therapy for refractory epilepsy.

We used the following search terms: (epilepsy OR seizure OR convulsion OR partial seizures OR generalized seizures OR refractory seizures) AND (ketogenic diet OR ketosis OR ketone OR diet therapy) AND (infant OR child OR adolescent) AND (cohort studies OR prospective study OR longitudinal study OR surveillance). The search strategy involved terms present either in the title/abstract or in the subject headings (only MEDLINE and CBM). The Cochrane Library of clinical trials was searched using the term "ketogenic diet".

The titles and abstracts of the retrieved studies were reviewed to exclude studies that were clearly irrelevant. Then, two authors independently read the full text of the remaining studies to assess their eligibility according to the inclusion criteria. Disagreements about the inclusion/exclusion of a study were discussed by the two authors to reach a consensus. In addition, the references of the included articles were searched manually to identify additional studies.

Study selection

The initial review included prospective studies written in either English or Chinese that reported the AEs or observed the possible AEs after using the classic or medium-chain triglyceride (MCT) KD to treat children with refractory epilepsy aged 0-18 years. Refractory epilepsy was defined as failure of seizure control despite use of two or more antiepileptic medications.

Data extraction and quality assessment

For each relevant study, demographic data, diet implementation, and detailed information about AEs and dropout were extracted. In this review, an AE was defined as any event, expected or otherwise, that occurred to the patient while on the diet. Quality assessment was performed according to the report of the following 6 elements: patient information (e.g., age, sex, etiology, type of seizures, pretreatment seizure frequency and number of pretreatment antiepileptic drugs), inclusion/exclusion criteria, diet information (e.g., fasting status, fluid restriction, calorie intake, protein intake, diet ratio, and supplementation of potassium citrate, multi-vitamins and minerals), reporting of AEs (e.g., method for monitoring AEs, detailed information of all AEs, severe AEs and death), auxiliary examination (e.g., blood test, ultrasound and electroencephalography), and retention and withdrawal (retention, lost to follow-up, and time and reasons of withdrawal). The first three elements [quality assessment 1 (QA1)] were used for the basic evaluation of all included studies, while the last three factors [quality assessment 2 (QA2)] did not apply to studies monitoring only specific possible AE (e.g., effects of KD on growth or vascular function). For each of these parameters, a score of 0 (no information), 1 (incomplete information) or 2 (complete information) was given. Therefore, the total score was six points for both QA1 and QA2. Studies with QA1 and QA2 scores ≥4 were assessed as high quality.

Data analysis

Categorical data were described as percentages. When calculating the percentages of AEs, sensitivity analysis was performed, limited to studies that scored >4 points in QA1 and provided complete information about AEs.

Results

Included studies and quality assessment

A total of 369 papers were identified in the initial search. After excluding 123 duplicate studies and 181 papers not eligible for the inclusion criteria, 65 prospective studies concerning the KD conducted since 1998 were identified. Subsequently, 13 were excluded because they included adults, five were excluded

because they did not mention any side effects, and two were excluded because their patient populations formed part of another two larger included studies (Fig.). Finally, 45 studies that met all of the inclusion criteria were evaluated in this review (Table 1).[5,7,11-54] Fourteen of the 45 studies were conducted in the USA, seven in China, four in India, three in the United Kingdom, two each in Italy, France, Sweden, Argentina, Korea and Turkey, and one each in Canada, Germany, Brazil, Egypt and the Netherlands. Of the included studies, nine were generated from seven randomized controlled trials (RCTs), while the rest of them were prospective observational studies. Study 14 was comprised of two separate studies; the research completed by Hemingway

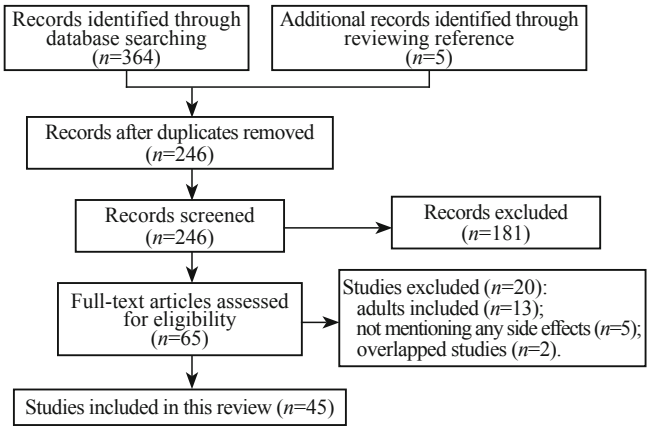

Fig. Flow diagram of study selection process.

Table 1. Characteristics and quality scores of the 45 prospective studies included for evaluation of safety and tolerability of the ketogenic diet in refractory childhood epilepsy

No.	Author/year	Design	*n*/M/F	Age (mean/range)	Diet/ratio	Fasting	Follow-up	QA1	QA2
1	Bergqvist et al, 2005[11]	RCT	48/34/14	5.3±2.7 y	Classical KD/4:1	Yes or no	3 mon	5	4
2	Seo et al, 2007[12]	RCT	76/43/33	4-16 y	Classical KD/3-4:1	No	3 mon	5	5
3	Neal et al, 2008[13]	RCT	75/42/33	2-16 y	Classical or MCT KD/ 3-5:1 or 40%-60%	No	12 mon	5	NA
4	Neal et al, 2009[14]	RCT	125/NR/NR	2-16 y	Classical or MCT KD/ 2-5:1 or 40%-60%	No	12 mon	6	4
5	Kang et al, 2011[15]	RCT	35/23/12	6-30 mon	Classical KD/3:1 initially	No	>2 y	5	3
6	Raju et al, 2011[16]	RCT	38/31/7	8 mon-5 y	Classical KD/2.5 or 4:1	No	3 mon	5	6
7	Christodoulides et al, 2012[17]	RCT	91/49/42	2-16 y	Classical or MCT KD/ 3-5:1 or 40%-60%	No	12 mon	6	NA
8	Hu et al, 2012[18]	RCT	60/45/15	21.5 mon	Classical KD/4:1	Yes	12 mon	6	4
9	El-Rashidy et al, 2013[19]	RCT	10/5/5	26±0.9 mon	Classical KD/4:1	NR	6 mon	5	6
10	Ballaban-Gil et al, 1998[20]	P	52/31/21	6.63 y	Classical KD/4:1	Yes	22 mon	4	NA
11	Vining et al, 1998[21]	P	51/34/17	4.7 y	Classical KD/4:1	Yes	12 mon	6	4
12	Furth et al, 2000[22]	P	112/59/53	5 y	Classical KD/NR	Yes	24 mon	3	NA
13	Lightstone et al, 2001[23]	P	46/26/20	5.3 y	Classical KD/4:1 or lower	NR	6 mon	4	NA
14	Freeman et al, 1998[24] /Hemingway et al, 2001[25]	P	150/85/65	5.3 y	Classical KD/3-4:1	Yes	3-6 y	4	3
15	Vining et al, 2002[26]	P	237/130/107	3.7 y	Classical KD/3-4:1	NR	3 y	3	NA
16	Liu et al, 2003[27]	P	25/15/10	6.9 y	Classical or MCT KD/ 3.5-4.3:1 or 40%-60%	Yes	4 mon	5	NA
17	Kwiterovich et al, 2003[7]	P	141/70/71	5.7 y	Classical KD/3-4:1	Yes	24 mon	4	NA
18	Hosain et al, 2005[28]	P	12/8/4	3 y	Classical KD/3-4:1	Yes	18 mon	5	5
19	Klepper et al, 2005[29]	P	15/4/11	5.2 y	Classical KD/3:1	NR	2-5.5 y	4	4
20	Caraballo et al, 2006[30]	P	11/7/4	5 y	Classical KD/4:1	Yes	≥18 mon	5	3
21	Rizzutti et al, 2007[31]	P	46/25/21	91 mon	Classical KD/4:1	Yes	≥12 mon	5	5
22	Nizamuddin et al, 2008[32]	P	137/NR/NR	0.3-14.8 y	Classical KD/3-4:1	Yes	4 y	4	NA
23	Bergqvist et al, 2008[33]	P	25/16/9	7.3±1.9 y	Classical KD/4:1	Yes or no	15 mon	6	NA
24	Nathan et al, 2009[34]	P	105/NR/NR	4 mon-18 y	Classical KD/2-4:1	Yes or no	6-60 mon	5	3
25	Sharma et al, 2009[35]	P	27/NR/NR	2.5 y	Classical KD/3-4:1	No	12 mon	5	6
26	Spulber et al, 2009[36]	P	22/13/9	5.5 y	Classical KD/4:1	Yes	12 mon	6	NA
27	Coppola et al, 2010[37]	P	38/22/16	37.2±16.5 mon	Classical KD/4:1	Yes	12 mon	5	4
28	Hong et al, 2010[38]	P	104/59/45	1.2 y	Classical KD/3-4:1	Yes or no	24 mon	4	4
29	Nabbout et al, 2011[39]	P	15/NR/NR	5 y	Classical KD/4:1	No	12 mon	4	3
30	Tagliabue et al, 2012[40]	P	18/8/10	12.4±5.6 y	Classical KD/3-4:1	Yes	6 mon	6	NA
31	Sharma et al, 2012[41]	P	27/NR/NR	2.5 y	Classical KD/3-4:1	No	12 mon	4	NA
32	Deng et al, 2012[42]	P	28/18/10	6 y	Classical KD/2-4:1	No	12 mon	5	5
33	Pires et al, 2013[43]	P	17/11/6	9.4±1.1 mon	Classical KD/3-4:1	No	6 mon	5	3
34	Lu et al, 2013[44]	P	83/49/34	5 mon-12 y	Classical KD/4:1	Yes	6 mon	4	5
35	Chinese Medical Association, 2013[5]	P	299/189/110	0.25-17.7 y	Classical KD/3-4:1	Yes	3 y	6	6
36	Li et al, 2013[45]	P	31/19/12	2.4 y	Classical KD/4:1	Yes	3 mon	5	5
37	Caraballo et al, 2014[46]	P	20/13/7	7.5 y	Classical KD/4:1	Yes	≥16 mon	4	3
38	Kayyali et al, 2014[47]	P	20/15/5	1.2±0.78 y	Classical KD/3-3.5:1	No	24 mon	4	3
39	Groleau et al, 2014[48]	P	24/14/10	5.5 y	Classical KD/4:1	Yes or no	15 mon	4	NA
40	Kapetanakis et al, 2014[49]	P	26/15/11	9 y	Classical KD/3-4:1	NR	24 mon	5	NA
41	Zhu et al, 2014[50]	P	20/14/6	42.5 mon	Classical KD/4:1	Yes	9 mon	5	6
42	Zhu et al, 2014[51]	P	36/24/12	44 mon	Classical KD/4:1	Yes or no	12 mon	5	4
43	Doksöz et al, 2015[52]	P	38/22/16	45.5 mon	Classical KD/3:1	No	6 mon	6	NA
44	Lambrechts et al, 2015[53]	P	48/32/16	1.3-17.5 y	MCT or classical KD	No	2 y	5	5
45	Doksöz et al, 2015[54]	P	38/22/16	45.5 mon	Classical KD/3:1	No	6 mon	6	NA

KD: ketogenic diet; MCT: medium-chain triglyceride; RCT: randomized controlled trial; P: prospective study; NR: not reported; NA: not available; QA1: quality assessment 1; QA2: quality assessment 2; M: male; F: female.

et al[25] in 2001 consisted of a 3-6-year follow-up of the 150 children enrolled in the study by Freeman et al[24] in 1998. The QA1 scores of the included studies ranged between 3-6, with 43 studies scoring 4-6 points. QA2 was performed for 28 studies, of which 20 studies scored ≥4 points (Table 1).

Only five studies assigned children to either the classic or MCT KD, and the remaining 40 articles assessed only the classic KD (Table 1). Information about the diet and fasting is also listed in Table 1. Generally, the ketogenic ratio in the classic KD was 2:1-5:1, while MCT in the MCT KD was 40%-60% of energy. Calorie intake ranged from 40 to 80 kcal/kg, or 75%-90% of the Recommended Dietary Allowance for calories, and the amount of protein provided was 1-2 g/kg/day. Most of the studies reported that these dietary parameters were adjusted during the course of follow-up, according to the child's growth, tolerance, urinary ketones, and seizure control.

Adverse effects

More than 40 categories of AEs associated with the KD were reported (Table 2). The most common AE after consuming the diet was gastrointestinal disturbances. Gastrointestinal discomfort included constipation, gastrointestinal disturbance, vomiting, diarrhea, hunger, abdominal pain, gastroesophageal reflux and fatty diarrhea, with constipation as the most frequent individual side effect. Following gastrointestinal symptoms in incidence were dyslipidemia (hyperlipidemia, hypercholesterolemia and hypertriglyceridemia), hyperuricemia, lethargy and infectious diseases. Severe AEs, such as respiratory failure, thrombocytopenic purpura and pancreatitis, were infrequent. Sensitivity analysis was conducted by excluding three studies that might not have provided complete AE information (scored 0-1 points in the element assessment); the recalculated AEs (data not shown) were not substantially different from the primary results listed in Table 2.

In addition, study 10[20] specifically reported five patients with serious complications after initiation of the diet: severe hypoproteinemia in two patients (one patient also developed lipemia and hemolytic anemia), renal tubular acidosis in one, and liver dysfunction in two (one patient had concomitant thrombocytopenia). Four of the five patients (80%) were simultaneously treated with valproate (VPA). One possible mechanism of the hypoproteinemia was an underlying inborn error of fatty acid metabolism, and the hepatotoxicity might have involved either impairment of fatty acid oxidation by VPA and/or the additive effect of the KD and VPA in the development of carnitine deficiency. The occurrence of renal tubular acidosis might also have been due to an adverse interaction between the KD and VPA.

Different KD regimens were compared in six RCTs (Table 3), with observation periods ranging from 3

Table 2. Reported adverse effects due to the ketogenic diet in prospective studies (n=1376)

Adverse effects	Number of cases (%)	Adverse effects	Number of cases (%)
Constipation	175 (13.2)	Osteopenia	17 (1.2)
Gastrointestinal disturbances	132 (9.6)	Irritability	12 (0.9)
Vomiting	125 (9.1)	Tachycardia	12 (0.9)
Hyperlipidemia	63 (4.6)	Gastroesophageal reflux	10 (0.7)
Hyperuricemia	61 (4.4)	Flushed face	10 (0.7)
Lethargy	56 (4.1)	Hematuria	9 (0.7)
Hypercholesterolemia	53 (3.8)	Aspiration pneumonia	7 (0.5)
Infectious disease	53 (3.8)	Behavioral problems	7 (0.5)
Hypoproteinemia	52 (3.8)	Respiratory failure	6 (0.4)
Diarrhea	52 (3.8)	Reduced carnitine levels	6 (0.4)
Hypertriglyceridemia	44 (3.2)	Reduction of plasm zinc	5 (0.4)
Acidosis	42 (3.1)	Epistaxis and bruising	4 (0.3)
Hunger	33 (2.4)	Thrombocytopenic purpura	3 (0.2)
Lack of energy/fatigue	32 (2.3)	Pancreatitis	2 (0.1)
Pneumonia	29 (2.1)	Gallbladder stones	2 (0.1)
Dehydration	29 (2.1)	Fatty liver	2 (0.1)
Elevation of liver enzymes	28 (2.0)	Fatty diarrhea	2 (0.1)
Hypoglycemia	25 (1.8)	Hair thinning	2 (0.1)
Abdominal pain	23 (1.7)	Pica	1 (0.07)
Electrolyte disturbance	22 (1.6)	Pulmonary edema	1 (0.07)
Weight loss	20 (1.5)	Shock	1 (0.07)
Fever	19 (1.4)	Dysphagia	1 (0.07)
Urolithiasis	19 (1.4)	Urinary sediment	1 (0.07)
Taste problems	17 (1.2)		

Table 3. The comparison of efficacy and tolerability of different ketogenic diet regimens in 6 randomized controlled trials

Study No.	Follow-up	Groups		Efficacy	Adverse effects
		1	2		
1[11]	3 mon	Fasting initiation of KD	Non-fasting gradual initiation of KD (the ketogenic ratio from 1:1 to 4:1)	Equivalent	Less weight loss, fewer and less severe episodes of hypoglycemia, and fewer treatments for acidosis and dehydration in group 2
2[12]	3 mon	4:1 diet	3:1 diet	Higher in group 1	Less gastrointestinal symptoms in group 2
4[14]	12 mon	Classical diet	MCT diet	Equivalent	Equivalent except increased reports of lack of energy and vomiting in group 1
5[15]	>2 y	Short-term KD for IS (6 mon)	Long-term KD for IS (>2 y)	Equivalent	No growth disturbance and osteopenia in group 1
6[16]	3 mon	4:1 diet	2.5:1 diet	Equivalent	Less constipation, weight loss and hospitalization for lower respiratory tract infections in group 2
8[18]	12 mon	Eating on demand	Eating at regular intervals	Equivalent; a faster onset of treatment action in group 1	Equivalent

KD: ketogenic diet; MCT: medium-chain triglyceride; IS: infantile spasms.

months to 2 years. Most of the paired KD regimens had equivalent efficacy. Non-fasting, gradual initiation of the KD caused less metabolic problems in the initial diet stage than fasting initiation, and a 2.5:1 or 3:1 ratio diet had fewer side effects than the classic 4:1 diet. In addition, when compared with a 2-year treatment, 6-month KD therapy for infantile spasm (IS) did not adversely influence growth or bone mineral content (BMC). Furthermore, similar AEs were observed with both the classic and MCT diets as well as with both eating on demand and eating at regular intervals.

Specific adverse effects

Ten studies observed specific side effects associated with the KD. In study 31,[41] the corrected QT interval did not change significantly over a 12-month period, as observed on serial electrocardiograms in 27 patients on the KD. Neither ST segment changes nor dysrhythmias were detected in any of the electrocardiograms.

In study 12,[22] six of 112 patients initiating the KD developed kidney stones during the follow-up period of 2 months to 2.5 years. Three patients had uric acid stones, and three patients had mixed calciumoxalate and uric acid stones. Patients maintained on the KD often had hypercalciuria, acid urine and low urinary citrate excretion. In conjunction with low fluid intake, these patients are at high risks of ureteral stone formation.

Study 23[33] measured the change in BMC using dual-energy X-ray absorptiometry for 25 children treated with the KD for 15 months; despite supplementation with vitamin D and calcium, both whole-body and spine BMC-for-age declined by 0.6 *Z* score/year, and whole-body and spine BMC-for-height declined 0.7 *Z* score/year and 0.4 *Z* score/year, respectively. Body mass index (BMI) *Z* score, age and ambulation were positive predictors of BMC, indicating worse BMC status for younger children and those who were not ambulatory or had a low BMI.

In addition to the 160 cases of dyslipidemia reported in the included literature (Table 2), two studies (studies 17 and 22)[7,32] specifically assessed the effect of the KD on blood lipid levels. In study 17, the high-fat KD significantly increased the mean plasma cholesterol, low-density lipoprotein, very low-density lipoprotein, triglyceride and total apolipoprotein B levels, and significantly decreased the mean high-density lipoprotein (HDL) level at 6-24 months of treatment. Therefore, the authors suggested that further studies should be conducted to determine if the KD adversely affects endothelial vascular function and promotes formation of atherosclerotic lesions. Study 22 found that the percentages of children with hyperlipidemia and low HDL increased after KD therapy. Moreover, children receiving a solely formula-based KD were less likely to have hypercholesterolemia than those eating solid food, probably due to the lower saturated fat content in the KD formulas.

Studies 40[49] and 45[54] evaluated the effects of the KD on vascular function. Carotid intima-media thickness and the carotid stiffness index did not significantly change after 6 or 12 months of KD treatment. Moreover, in study 45, elastic properties of the aorta did not change at month 6 of therapy. In study 40, a decrease in carotid distensibility was seen at 12 months, when compared with baseline values. However, the difference was not significant at 24 months. In addition, study 43[52] showed a decrease in the peak late atrial filling velocity/peak early right ventricular filling velocity ratio, early diastolic myocardial velocity, and early/late diastolic myocardial velocity ratio gathered from the tricuspid annulus at month 6, compared with baseline, indicating that the KD might be associated with right ventricular diastolic dysfunction.

Study 16[27] demonstrated that the nutrient intakes of children on the classic or MCT KD, including daily multivitamin and mineral supplements, met or exceeded the dietary reference intakes (DRIs) for most nutrients (vitamins A, B1, B2, B3, B6, B12, C and D; calcium; ferrum; magnesium and zinc) except phosphorus (68% and 76% of the DRI in the classic and MCT KD, respectively) and folate (59% of the DRI in the classic diet). In addition, both diets had inadequate amounts of most micronutrients without the addition of vitamin and mineral supplements. Study 7[17] examined vitamin and mineral levels in 91 patients at baseline and after 12 months on the classic or MCT KD; with supplementation of additional vitamins and minerals, the mean plasma vitamin A level decreased in the classic group but increased in the MCT group. Mean plasma vitamin E levels increased in both groups. No significant change was observed for plasma zinc level, but both mean plasma selenium and magnesium levels decreased in the KD group as a whole. The changes in vitamin and mineral levels suggest that micronutrient status might be suboptimal.

Effect of the ketogenic diet on growth

Four of the included studies specifically evaluated the impact of the KD on growth in children, and another six studies provided data about growth. Pre- and post-diet weight, height and BMI are listed in Table 4. To assess growth, most studies used *Z* scores, which represent an individual's measured value in terms of the standard deviation (SD) from the mean. Thus, a child exactly at the average height or weight for age and sex would have a *Z* score of 0, and a child in the 97.5th percentile would have a *Z* score of +2 (i.e., 2SD above the mean). The results from the different studies were inconsistent. Two studies found that the diet had a positive or partially

positive effect on growth (studies 9 and 43),[19,52] while another six studies concluded that the diet had a negative or partially negative impact on growth (studies 3, 15, 16, 23, 26 and 39).[13,26,27,33,36,48] In two studies, the changes in growth after the diet were not statistically significant (studies 19 and 30).[29,40] Because the population characteristics, diet prescriptions, observation periods and measured parameters varied among these studies, it was not appropriate to perform combined analysis. The lowest mean *Z* score was -1.39, measured for height in study 23 (i.e., not exceeding 2SD below the mean).[33]

In addition, two studies assessed the effects of the KD on resting energy expenditure (REE) and substrate oxidation.[40,48] The REE represents 50%-70% of an individual's total daily energy expenditure. There was no change in REE after 6 (study 30) or 15 (study 39) months of KD treatment.[40,48] The respiratory quotient decreased significantly in both studies.

Retention rates and reasons for discontinuation of the diet

The 23 studies that reported the number of patients remaining on the diet at different time points were included in the calculation of retention rates (Table 5). The total retention rates at 1 year and 2 years were 45.7% and

Table 4. Changes in anthropometric nutritional parameters while on the ketogenic diet in prospective studies

Study No.	Follow-up	*n*	Weight (mean±SD)		Height (mean±SD)		BMI (mean±SD)		Conclusion
			Pre-diet	Post-diet	Pre-diet	Post-diet	Pre-diet	Post-diet	
9[19]*	6 mon	10	NA	NS	NA	NA	NA	Increase	Weight: NS BMI: increase
16[27]†	4 mon	25	Classical KD: 48.6±42.1 MCT: 54.0±42.3	Classical KD: 39.1±39.7 MCT: 44.5±40.0	Classical KD: 42.8±37.7 MCT: 53.0±30.3	Classical KD: 42.0±34.7 MCT: 52.1±32.6	NA	NA	Height: NS Weight: decrease (classical KD)
19[29]	2-5.5 y	15	NA	NS	NA	NS	NA	NA	NS
30[40]*	6 mon	18	-0.81±2.42	-0.86±2.47	-0.72±1.70	-0.76±1.73	-1.33±2.17	-1.10±2.11	NS
43[52]	6 mon	38	14.8 (9.3)‡ kg	16.3 (10.4)‡ kg	102.1±22 cm	105±22.5 cm	15.9±2.3 kg/m^2	17.2±6.4 kg/m^2	Increase
3[13]*	12 mon	75	0.17224±1.478935	-0.18950±1.532253	-0.10061±1.351129	-0.50212±1.491335	0.41112±1.346118	0.26182±1.349311	Weight/height: decrease
15[26]*	3 y	237	NA	Decrease	NA	Decrease	NA	NA	Decrease
23[33]*	15 mon	25	-0.23±1.69	-1.02±1.27	-0.31±1.21	-1.39±1.08	-0.06±1.57	-0.20±0.92	Weight/height: decrease BMI: NS
26[36]*	12 mon	22	-0.65±2.13	-1.17±1.62	-0.77±2.27	-1.14±2.09	-0.21±1.10	-0.71±1.04	Decrease
39[48]*	15 mon	15	-0.9±1.4	-0.86±0.50	-0.6±0.9	-1.2±0.6	-0.8±1.6	0±1.1	Weight: NS Height: decrease BMI: increase

*: values are given as *Z* score; †: values are given as percentile; ‡: values are given as median (interquartile range). KD: ketogenic diet; BMI: body mass index; SD: standard deviation; NS: not statistically significant; NA: not available.

Table 5. Retention rates of the ketogenic diet reported in prospective studies (*n*=1504)

Study No.	*n*	On diet					
		3 mon	6 mon	12 mon	24 mon	36 mon	48 mon
9[19]	10	-	8	-	-	-	-
20[30]	11	-	-	6	5	-	-
18[28]	12	-	-	10	9	-	-
29[39]	15	-	-	5	-	-	-
33[43]	17	-	17	-	-	-	-
37[46]	20	16	15	15	14	-	-
38[47]	20	20	18	17	8	-	-
25[35]	27	24	15	10	-	-	-
32[42]	28	19	10	5	-	-	-
36[45]	31	31	-	-	-	-	-
41[50]	36	26	17	11	-	-	-
6[16]	38	32	-	-	-	-	-
21[31]	46	40	33	33	-	-	-
13[23]	46	-	27	-	-	-	-
1[11]	48	42	-	-	-	-	-
44[53]	48	39	-	16	11	-	-
8[18]	60	-	-	37	-	-	-
2[12]	76	-	65	-	-	-	-
28[38]	104	86	76	47	28	-	-
4[14]	125	100	80	-	68	-	-
14[24,25]	150	125	106	83	58	30	19
15[26]	237	-	-	135	-	-	-
35[5]	299	197	134	79	29	7	-
Retention rates (%)		78.1 (797/1020)	61.9 (621/1004)	45.7 (509/1113)	29.2 (230/789)	8.2 (37/449)	12.7 (19/150)

"-": no data.

Table 6. Reasons for discontinuing the ketogenic diet reported in prospective studies (n=838)

Reasons	Number of cases (%)	Reasons	Number of cases (%)
Lack of efficacy	418 (49.9)	Weight loss	2 (0.2)
Too restrictive	93 (11.1)	Pancreatitis	2 (0.2)
Poor compliance complications	91 (10.9)	Lethargy	1 (0.1)
Illness	46 (5.5)	Hypoglycemia	1 (0.1)
Refusal to eat	40 (4.8)	Aspiration pneumonia	1 (0.1)
Lack of efficacy/too restrictive	32 (3.8)	Hyperlipidemia	1 (0.1)
Seizure free/>90% improvement	32 (3.8)	Ureteral stones	1 (0.1)
Lost to follow up	27 (3.2)	Fever	1 (0.1)
Gastrointestinal discomforts	20 (2.4)	Epilepsy surgery	1 (0.1)
Infections	12 (1.4)	Acute respiratory distress	1 (0.1)
Intolerance	10 (1.2)	Unstable ketone levels	1 (0.1)
Hypoproteinemia	4 (0.5)		

29.2%, respectively. Approximately 10% of children were still on the diet at 3 or 4 years.

The reasons for discontinuation of the diet were reported for 838 patients (Table 6). Nearly half of the children discontinued the diet because of lack of efficacy; about 11% of the patients or their caregivers found the diet too restrictive. Collectively, 54.8% of the 838 patients discontinued the KD for either of these two reasons. Side effects were not the main reason for KD discontinuation.

Deaths

In the included literature, 24 deaths after diet initiation were reported. The deaths resulted from aspiration pneumonia, diabetes mellitus, severe infection, arrhythmia and shock, drowning, nocturnal seizure, asphyxia due to sputum blockage, or perforated gastric ulcer after epilepsy surgery for one case each; accidental injuries for two cases; severe pneumonia or status epilepticus for three cases each. The causes of the remaining 8 deaths were not reported. Seven deaths occurred after stopping the diet, and no death was attributed to the KD in the literature.

Discussion

The KD is being more frequently used worldwide as an alternative treatment for intractable childhood epilepsy. The included studies were conducted in 15 different countries distributed across North and South America, Europe, Asia and Africa. Accordingly, the results of this review reflect, to some extent, the effects of the diet on a global basis. In addition, the patients enrolled in the studies ranged from 3 months to 18 years of age, and the observational periods lasted from 3 months to 5 years. Therefore, in this review, we were able to summarize the currently known short- and long-term impacts of KD on children of all age groups. Nevertheless, ethnic differences should be considered when using the results from this review for reference.

The KD is a relatively safe and tolerable dietary therapy for children with refractory epilepsy. Although a series of AEs have been reported in the included studies, severe AEs occurred very rarely. To ensure safe implementation of KD treatment, we suggest that children on this diet should be followed up regularly and monitored for possible AEs.

Keene[3] summarized adverse events of the KD intervention for children in a systematic review in 2006. In this study, a total of 13 types of adverse reactions were extracted from 10 small case series or individual case reports; vomiting and elevated serum lipid levels were the most common AEs identified. Recently, Martin et al[55] also systematically reviewed the KD for epilepsy. They included 7 RCTs which recruited children and adolescents, and revealed that the main adverse effects of the classical KD were gastrointestinal symptoms. In the present review, similar results were found and we further made a detailed list of the series of adverse effects reported in prospective studies and calculated their frequency respectively.

Several RCTs about the KD therapy have been published since 2005, which may help physicians to choose more secure KD regimens with the same efficacy. Based on the results from RCTs, it is reasonable and more acceptable to initiate the KD gradually, without fasting, and based on demand from the patient. To increase the tolerability of the KD, the 4:1 diet can be adjusted to 3:1 or 2.5:1. Moreover, to avoid the associated long-term risks, short-term KD therapy for patients with IS is justified.

Whether the KD has an adverse impact on growth rate remains controversial, even after this review. Most of the studies showing negative effects had an observational period >12 months. In contrast, the follow-up periods for the four studies without negative impacts were 4 or 6 months, except that of study 20 (2-5 years). It is possible that the adverse influence of the KD on growth emerges after a longer interval. Therefore, growth status should be regularly monitored for children receiving long-term KD therapy (e.g., >12 months).

Although the reported deaths were believed to be unrelated to the KD, it should be noted that quite a few of the patients on the diet have profound disabilities and are very vulnerable,[24,25] namely susceptible to infections, aspiration and organ dysfunction. Therefore, during KD treatment, careful medical supervision should be emphasized for these fragile patients.

In the review by Martin et al,[55] only RCTs were included and the drop-outs of the classic KD ranged from 10%-20% over a three- to six-month trial period.

In our review, the retention rates from 3 months to 4 years were calculated. It is demonstrated that the drop-outs increased along with the treatment time, and the attrition rates were higher than those observed in RCTs. Martin et al[55] also concluded that adverse effects were common reasons for participants dropping out of trials. The short duration of RCTs included in the above mentioned review likely impacted patients' decisions to stay on the diet and wait for its efficacy, and patients often stop the diet due to intolerable adverse events. However, when more prospective studies with longer duration were included for analysis in this review, it was revealed that the most common reasons for drop-out was lack of efficacy, while AEs were no longer a prominent cause resulting in the KD discontinuation.

Based on this review, there are unresolved questions about the safety of the KD. First, a number of serious AEs occurred, but it is not certain whether these side effects are truly due to the treatment or perhaps an underlying disorder. Future large, randomized controlled trials are needed to address this question; Second, long-term follow-up is needed to observe whether temporarily elevated lipid levels while on the KD cause patients to develop atherosclerosis or cardiovascular disease later in life; Finally, catch-up growth might occur after discontinuation of the diet.[56] Thus, to evaluate long-term growth outcomes, children should be followed up for years, even after stopping the diet.

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