REVIEW

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Efficacy of ketogenic diet therapy in infants with epilepsy: A systematic review and meta-analysis

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ABSTRACT

Introduction: The ketogenic diet therapy, a high-fat, low-carbohydrate diet, has been known since the 1920s as a therapeutic option in treating drug-resistant epilepsy. However, with the increasing incidence of the infant population, research on this subject is still limited. This systematic review and meta-analysis aimed to evaluate the efficacy of ketogenic diet therapy in infants with epilepsy.

Methods: We searched the articles from Cochrane Library, Embase, Pubmed, ScienceDirect, and Scopus, based on predetermined inclusion criteria. Four investigators independently performed screening, study selection, extracted data, and assessed the quality of relevant articles. We used the Newcastle-Ottawa Quality Assessment Scale to assess the risk of bias in included articles. We present the results of the meta-analysis using a forest plot.

Results: We identified 1781 studies from database screening, with eight cohort studies in this study. Our meta-analysis revealed that an estimate of 69% of infants with epilepsy achieved ≥50% seizure reduction in three months follow-up (95% confidence interval [CI] 56- 82%) and an estimate of 36% of infants achieved seizure freedom (95% confidence interval [CI] 20- 51%). Retention rates ranged from 91% at three months to 28% at 24 months. The most common side effects reported were dyslipidemia (131/355, 36.9%), gastrointestinal disturbances (66/355, 18.6%), and hyperkeratosis/acidosis (42/355, 11.8%).

Conclusion: Ketogenic diet therapy is well tolerated and effectively reduces seizure frequency at three months in infants with epilepsy.

Keywords: epilepsy, infants, ketogenic diet therapy.
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INTRODUCTION

Epilepsy is one of the most common diagnoses encountered by pediatric neurologists. Identifying the type of epilepsy syndrome through EEG results and the clinical picture is essential to determine the etiology, management, and prognosis.[1,2] The incidence of epilepsy in children varies quite widely in Western countries compared to developing countries, namely around 33.3-82/100,000 cases per year in Western countries and around 187/100,000 cases per year in developing countries, with the highest incidence rate at the first year of life, is 102/100,000 cases per year.[3]

Most children with epilepsy respond to treatment and are free of seizures. However, some children do not respond adequately to currently available treatments, developing drug-resistant epilepsy. According to the International League Against Epilepsy (ILAE), drug-resistant epilepsy is 'failure of adequate trials of two antiepileptic drugs (AEDs) that are tolerated, properly selected and used'. The prevalence of children with drug-resistant epilepsy is estimated at 30%. One that has been widely studied as a treatment option for DRE in children is ketogenic diet therapy (KDT).[4,5]

The ketogenic diet therapy is a high-fat, low-carbohydrate diet designed to mimic the fasting state. The use of KDT has grown since 1911, but its use has decreased since the emergence of various antiepileptic drugs. In the modern era, KDT began to develop again in 1994, where the story of a boy named Charlie with DRE was able to control his seizures using KDT.[6] Various RCTs have also proven the effectiveness and safety of KDT in treating DRE.[7,8,9] However, data regarding the use of KDT in infants under two years of age is still limited. This systematic review and meta-analysis aimed to evaluate the efficacy of ketogenic diet therapy in infants with epilepsy. Our meta-analysis focused on the efficacy of KDT in infants with epilepsy, but we also reviewed the safety of KDT in this particular population group.

METHODS

We conducted a systematic review and meta-analysis based on PRISMA guidelines. Several databases, including Cochrane Library, Embase, PubMed, ScienceDirect, and Scopus, were searched with the following keywords, summarized in Table 1. The search included data up until April 27, 2023.

Inclusion Criteria, Study selection, and Data extraction

We included RCTs and observational cohort studies that fulfilled the inclusion criteria: full-text articles published online in English from 2013 onwards, at least one participant in the study age 0-24 months or was stated as "infant". If the study included participants of varying ages, they should clearly separate and specify the data for each age group, and the KDT should last

Table 1. **Database search strategy keywords**

Database	Search keywords
Cochrane Library	(infant) AND (epilepsy) AND (ketogenic diet) AND (seizure frequency)
Embase	('infant'/exp OR infant) AND ('epilepsy'/exp OR epilepsy) AND ('ketogenic diet'/exp OR 'ketogenic diet' OR (ketogenic AND ('diet'/exp OR diet))) AND ('seizure frequency'/exp OR 'seizure frequency' OR (('seizure'/exp OR seizure) AND ('frequency'/exp OR frequency)))
PubMed	(infant) AND (epilepsy) AND (ketogenic diet) AND (seizure frequency)
ScienceDirect	(infant) AND (epilepsy) AND (ketogenic diet) AND (seizure frequency)
Scopus	TITLE-ABS-KEY (infant) AND (epilepsy) AND (ketogenic diet) AND (seizure frequency)

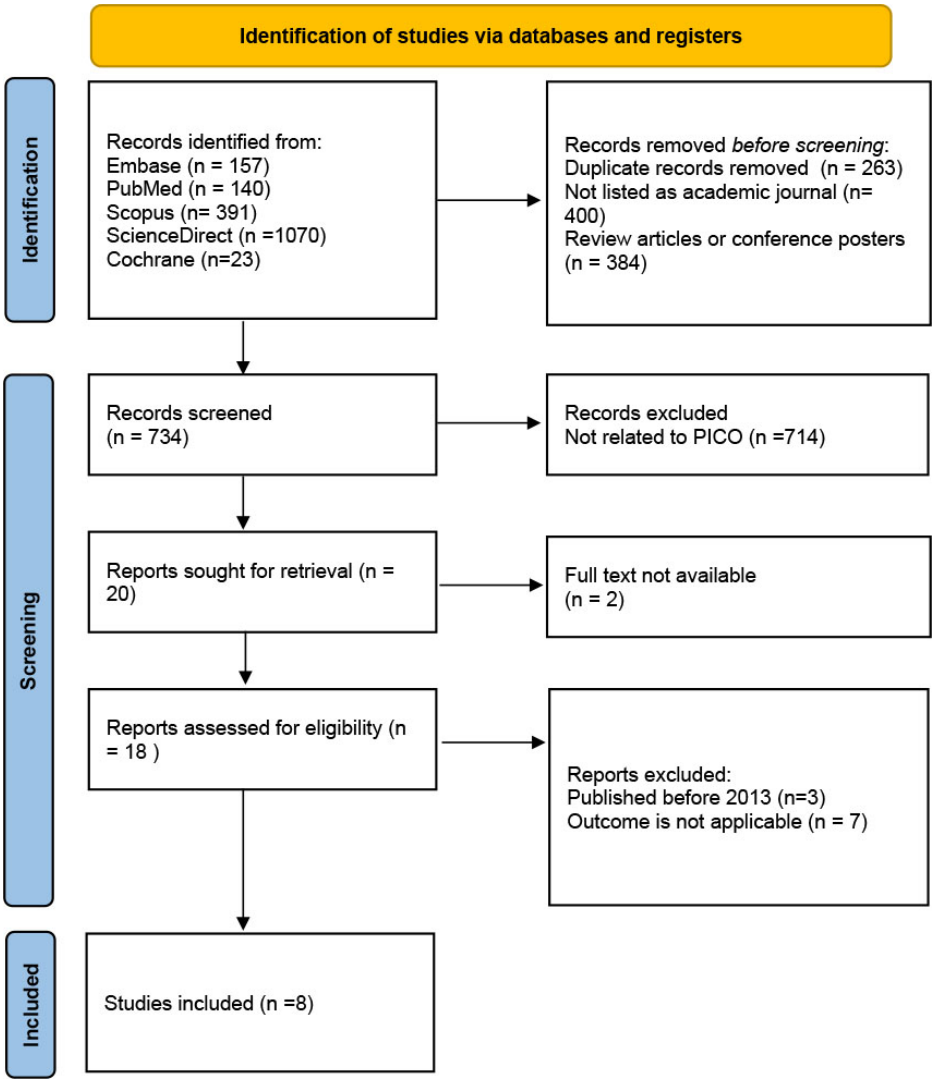

Figure 1. PRISMA flowchart on the literature search and screening process.

for a minimum of one month. All types of KDT were included without exception. We removed duplicates from the first results on all the databases.

Four investigators independently screened the titles and abstracts to assess article eligibility based on predetermined inclusion criteria. Disagreements were resolved through deliberation. The relevant data were collected using a comprehensive data extraction form including the following information: (1) first author's surname; (2) study and publication year; (3) design of the study; (4) population involved in the study; (5) clinical setting of the study; (6) type of epilepsy/seizure; (7) number of infants who initiated the diet; (8) type of ketogenic diet used; (9) seizure outcomes at 1, 3, 6, 12, and 24 months; (10) seizure outcomes at other unspecified time points; (11) rates of retention in the study; and (12) adverse side effects experienced by infants.

Quality Appraisal

We used the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies to assess the risk of bias in included articles. This checklist comprises three domains of questions based on selection, comparability, and outcome. The selection domain consists of four questions: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of the study. The comparability domain consists of one question whether the cohort is comparable based on the design or analysis. This domain of question allows for a maximum allocation of two stars. The outcome domain consists of three questions: the outcome assessment, whether the follow-up was long enough for outcomes to occur, and the adequacy of the follow-up of cohorts. Based on AHRQ standards, the Newcastle-Ottawa scales can be converted to good quality if there are 3-4 stars in the selection domain and 1-2 stars in the comparability domain, and 2-3 stars in the outcome domain. The article has fair quality if there are 2 stars in the selection domain, 1-2 stars in the comparability domain, and 2-3 stars in the outcome domain. Poor quality is considered if there is only 0-1 star in the selection domain or 0 stars in the comparability domain, or 0-1 star in the outcome domain.[10]

Outcomes

The primary outcome of this study was the efficacy of KDT for epilepsy in infants aged 0-24 months. The efficacy was measured by determining the number or percentage of infants who achieved a seizure reduction

of 50% or more after a follow-up period of at least one month. The secondary outcomes were seizure freedom rates within one month of follow-up onwards, retention rates, and side effects.

Data Analysis

Our statistical analysis was carried out using OpenMetaAnalyst. Heterogeneity was assessed through the evaluation process by Mantel–Haenszel χ 2 test and the I 2 statistic. A fixed-effects model was utilized if the I2 value was below 50%, indicating acceptable heterogeneity. On the other hand, if the I2 value exceeded 50% (indicating high heterogeneity), a random-effects model was employed. The statistical significance of the results was determined by a p-value below 0.05.

RESULTS

We identified 1781 studies by screening five databases. Out of these, 1047 studies were removed: 263 were duplicates, 400 were not listed as academic journals, and 384 were review articles or conference posters. We then screened and assessed compatibility with PICO for 734 studies. Among them, only 20 studies remained for retrieval, while two studies were excluded because full texts were not available. Finally, 18 studies were assessed for eligibility, of which eight studies met our inclusion criteria. (Figure 1).

Study Characteristics

Out of the eight studies included in this review involving 366 infants, five were cohort retrospective studies, and three were cohort prospective studies. Table 1 presents the summary descriptive data of the studies included.

Most studies involved infants with various epilepsy syndromes, with only one specifically focusing on infants with infantile spasms. Three out of the eight studies specifically included infants with refractory epilepsy. From six studies, 56% of the infants were male (161/286), and the mean age at which they started the ketogenic diet was 8.64 months, as reported by all eight studies. The types of ketogenic diets used varied among the studies, including the classic ketogenic diet (with ratios of 4:1, 3.5:1, 3:1, 2.5:1, 2:1) and modified ketogenic diets such as the modified Atkins diet (MAD), and medium chain triglyceride diet (MCT). Information on the proportion of ketogenic diets used was provided in five studies, which revealed that 86% of the infants (232/268) used the classic ketogenic diet, with a majority of them following a 3:1 ratio (63.8%). Additionally, 13% of the infants (34/268) used MAD, while only 0.7% (2/268) used MCT.

Study Quality

The risk of bias was assessed from available full text using Newcastle-Ottawa Quality Assessment Form for Cohort studies. The elements are given in Figure 2. All included studies were rated as "good" quality. Only one study describes the non-exposed cohort selection from the same community as the exposed cohort.

Efficacy of Ketogenic Diet Therapy

Data were available from 8 studies involving a total of 366 infants. The total number of infants analyzed varied because efficacy rates were not presented at the same time point in each study.

After one month, 56 out of 89 infants (63%) achieved ≥50% seizure reduction (range 29%-83%; median 72%; IQR 20%), and 11 out of 42 infants (26%) achieved seizure-free status (range 20%-35%; median 28%; IQR 8%).

After three months, 239 out of 335 infants (71%) achieved ≥50% seizure reduction (range 29%-88%; median 67%; IQR 19%), and 118 out of 288 infants (41%) achieved seizure-free status (range 20%-65%; median 40%; IQR 24%).

After six months, 192 out of 251 infants (76%) achieved ≥50% seizure reduction (range 0%-94%; median 79%; IQR 21%), and 102 out of 251 infants (41%) achieved seizure-free status (range 19%-60%; median 35%; IQR 22%).

After 12 months, 166 out of 212 infants (78%) achieved ≥50% seizure reduction (range 41%-100%; median 89%; IQR 12%), and 95 out of 189 infants (50%) achieved seizure-free status (range 18%-81%; median 33%; IQR 35%).

After 24 months, out of 35, 27 infants (77%) achieved ≥50% seizure reduction (range 67%-100%; median 86%; IQR 17%), and ten infants (29%) achieved seizure-free status (range 19%-57%; median 29%; IQR 19%).

One study that presented efficacy rates at an unspecified time point reported that 2 out of 24 (8%) achieved seizure-free status.

Meta-analysis

From the analysis of eight studies, the pooled response proportion for infants who achieved ≥50% seizure reduction at three months or an unspecified time was 0.69 (95% CI 0.56-0.82), with high heterogeneity (I^2=87.19%, p <0.001). Due to high heterogeneity, a binary random-effects model was applied. These results indicate that approximately 69% of infants treated with ketogenic diet therapy will experience ≥50% seizure reduction at three months or an unspecified time.

Based on the analysis of seven studies, the pooled response proportion from these studies was 0.36 (95% CI 0.2-0.51), and there was a high level of heterogeneity (I2=89.39%, p <0.001). A binary random-effects model was used to account for this heterogeneity. These findings suggest a significant percentage (36%) of infants can experience relief from seizures by implementing ketogenic diet therapy at three months or an unspecified time.

Retention Rates

The minimum duration of treatment with the ketogenic diet was one month, and the longest was 60 months. Seven studies were included for calculating the retention rate of KD at months 3, 6, 12, and 24, respectively. The retention rates were 253 out of 279 (91%) at three months, 226 out of 308 (73%) at six months, 154 out of 262 (59%) at 12 months, and 35 out of 124 (28%) at 24 months.

All individuals in the included studies were receiving a classical KD, except for n = 2 on a KD-MCT (Ketogenic Diet with Medium-Chain Triglycerides) with unknown duration, n = 34 on a MAD (Modified Atkins Diet) with unknown duration, and four individuals switched diet therapy from KD or MCT to MAD.

Reasons for diet discontinuation were given below (we calculated the percentages using the total number of individuals whose reasons for diet discontinuation were reported in each study):

Table 2. Summary descriptive data of the studies included

Study	Design study	Study population	Clinical setting	Epilepsy/ seizure type	Number of participants starting the diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%)	Seizure outcome (6 mo), n (%)	Seizure outcome (12 mo), n (%)	Seizure outcome (other), n (%)	Retention, n(%)
Pires ME et al 2013[11]	Cohort prospective	17 patients with IS refractory to vigabatrin (VGB) and hydrocortisone (HC)	Robert-Debré Hospital, Paris & University Hospital, Amiens	Symptomatic infantile spasms, n= 9 Cryptogenic infantile spasms, n= 8	17 (mean age 9.4 ± 1.1 months)	Classic ketogenic diet 4:1 or 3:1 ratio	2 (11.8%) <50% seizure reduction 15 (88.2%) ≥50% seizure reduction 11 (64.7%) seizure free	2 (12.5%) <50% seizure reduction 14 (87.5%) ≥50% seizure reduction 9 (56.3%) seizure free		1 mo: 4 (23.5%) <50% seizure reduction 13 (76.4%) ≥50% seizure reduction 6 (35.2%) seizure free	17 (100%) on diet at 3 mo 16 (94.1%) on diet at 6 mo
Dressler A et al 2015[12]	Cohort retrospective	115 children with epilepsy treated with KD at the Medical University Vienna from March 1999-April 2014 (divided into group A (<1,5 years, n=58) and group B (>1,5 years, n=57)	Medical university vienna, department of pediatrics	Infantile spasms, n=59 Lennox–Gastaut syndrome, n=20 Dravet syndrome, n=10 Partial epilepsy, n=10 Idiopathic generalized epilepsy, n=6 Progressive myoclonic epilepsy, n=3 Myoclonic astatic epilepsy, n=2 Ohtahara syndrome, n=2 CSWS, n=2 Pseudo-Lennox syndrome, n=1	58 (mean age 0.68 ± 0.45 years)	Classic ketogenic diet 4:1, 3:1, 3.5:1, 2.5:1, and 2:1 ratio.	37 (63.7%) >50% seizure reduction 20 (34.4%) seizure free	32 (55.1%) >50% seizure reduction 19 (32.7%) seizure free	27 (46.5%) >50% seizure reduction 19 (32.7%) seizure free	>12 mo: 9/18 (50%) seizure free	
Ismayilova N et al 2018[13]	Cohort retrospective	All infants (<2 years old) with medication-refractory epilepsy were treated with KD at the Evelina London Children's Hospital between 2006 and 2016.	Evelina London Children's Hospital	Symptomatic epilepsy, n= 15 Idiopathic epilepsy, n=14	29 (2.5 weeks- 23 months)	Classic 3:1 ketogenic diet (28/29) and MCT (1/29)	3 (12.5%) <50% seizure reduction 7 (29.2%) >50% seizure reduction	3 (30%) <50% seizure reduction		1 mo: 7 (29.2%) >50% seizure reduction At unknown time point: 2 (8.3%) seizure free	24 (83%) on diet at 1 mo 10 (34%) on diet at 6 mo

Study	Design study	Study population	Clinical setting	Epilepsy/ seizure type	Number of participants starting the diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%)	Seizure outcome (6 mo), n (%)	Seizure outcome (12 mo), n (%)	Seizure outcome (other), n (%)	Retention, n(%)
Wirrell E et al. 2018[14]	Cohort retrospective	All infants less than 12 months of age with epilepsy and treated with a ketogenic diet at Mayo Clinic, Rochester, between September 1, 2007, and July 31, 2016,	Mayo Clinic Rochester,	Focal spasm, n=18 Epileptic spasm, n=13	26 (median age 7 months (range 5-11 months))	Classic ketogenic diet 2:1 ratio (26),	16 (80%) ≥50% seizure reduction 9 (45%) seizure free	14 (82.3%) ≥50% seizure reduction 5 (29.4%) seizure free	10 (91%) ≥50% seizure reduction 3 (27.3%) seizure free	1 mo: 17 (68%) ≥50% seizure reduction 5 (20%) seizure free 24 mo: 6 (85.7%) ≥50% seizure reduction 2 (28.6%) seizure free	25 (96.1%) on a diet at 1 mo 20 (77%) on diet at 3 mo 17 (65.4/%) on diet at 6 mo 11 (42.3%) on diet at 12 mo 7 (27%) on diet at 24 mo
Riantarini I et al 2019[15]	Cohort retrospective	115 infants with epilepsy treated with a ketogenic diet or Modified Atkins Diet (MAD) from January 1, 2006, to June 30, 2016, at Severance Children Hospital, South Korea	Severance Children Hospital, South Korea	Infantile spasms, n= 92 Infantile epileptic encephalopathy, n= 13 Early myoclonic encephalopathy, n= 1 Migrating focal seizures in infancy, n= 2 Severe myoclonic epilepsy in infancy, n=3 Unclassified generalized epilepsy, n=1 Unclassified focal epilepsy, n=3	115 (mean 7.5 ± 2.7 months)	Classic ketogenic diet 3:1 ratio (73 (63%)), Modified Atkins Diet (MAD) (34 (30%)), and classic ketogenic diet 4:1 ratio (8 (7%)).	12 (11.5%) <50% seizure reduction 29 (27.9%) 50-89% seizure reduction 5 (4.8%) ≥ 90% seizure reduction 58 (55.8%) seizure free	5 (5.9%) <50% seizure reduction 15 (17.9%) 50-89% seizure reduction 14 (16.7%) ≥ 90% seizure reduction 50 (59.5%) seizure free	4 (5.7%) <50% seizure reduction 7 (10%) 50-89% seizure reduction 2 (2.9%) ≥ 90% seizure reduction 57 (81.4%) seizure free		104 (90.4%) on diet at 3 mo 84 (73%) on diet at 6 mo 70 (60.9%) on diet at 12 mo

Study	Design study	Study population	Clinical setting	Epilepsy/ seizure type	Number of participants starting the diet (age range)	Ketogenic diet type	Seizure outcome (3 mo), n (%)	Seizure outcome (6 mo), n (%)	Seizure outcome (12 mo), n (%)	Seizure outcome (other), n (%)	Retention, n(%)
Armeno M et al 2021[16]	Cohort prospective	Infants < 2 years with drug-resistant epilepsy treated with CKD at Hospital de Pediatría Garrahan between February 2013 and September 2020	*Hospital de Pediatria J.P. Garrahan, Buenos Aires, Argentina*	West syndrome, n=30 Migrating focal seizures, n=7 Dravet syndrome, n=4 Ohtahara syndrome, n=2 Myoclonic epilepsy, n=1 Infantile spasms without hypsarrhythmia, n=1	56 (median 12.23 months (1.73-25.87)	Classic ketogenic diet 4:1 ratio of 4 (7.1%), 3:1 ratio of 30 (53.6%), 2.5:1 ratio of 7 (12.5%), 2:1 ratio of 14 (25%), and 1:1 ratio of 1 (1.8%)	35 (62.4%) >50% seizure reduction 11 (19.6%) seizure free	34 (65.4%) >50% seizure reduction 10 (19.2%) seizure free	27 (79.4%) >50% seizure reduction 6 (17.6%) seizure free	24 mo: 14 (66.7%) >50% seizure reduction 4 (19%) seizure free	56 (100%) on diet at 3 mo 52 (92.8%) on diet at 6 mo 34 (60.7%) on diet at 12 mo 21 (37.5%) on diet at 24 mo
Liu Y et al. 2021[17]	Cohort prospective	Children with refractory epilepsy (divided into the A (6-12 mo), B (12-24 mo), C (24-36 mo) groups)	*Children's Hospital of Chongqing Medical University*		23 (9 group A (mean age 8.00±3.32 months) and 14 group B (mean age 16.6±3.05 months)	Classic ketogenic diet (2:1- 4:1)	7 (30.4%) <50% seizure reduction 13 (56.5%) 50-90% seizure reduction 3 (13%) 90-99% seizure reduction	5 (21.7%) <50% seizure reduction 15 (65.2%) 50-90% seizure reduction 3 (13%) 90-99% seizure reduction	3 (13%) <50% seizure reduction 16 (69.6%) 50-90% seizure reduction 4 (17.4%) 90-99% seizure reduction	1 mo: 4 (17.4%) <50% seizure reduction 15 (65.2%) 50-90% seizure reduction 4 (17.4%) 90-99% seizure reduction	23 (100%) on diet at 3 mo, 6 mo, 12 mo
Ruiz-Herrero J et al 2021[18]	Cohort retrospective	All the infants with epilepsy on a KDT at the Niño Jesús Pediatric Hospital of Madrid (Spain) between January 2000 and December 2018	Niño Jesús Pediatric Hospital of Madrid	Tonic seizure, n= 33,3% Focal onset seizure, n= 26,2% Various types, n=14,3% Generalized tonic-clonic seizure, n=4 Myoclonic seizure, n=3 Clonic seizure, n=2	42 (median 7.7 months (4.5- 16.7 months)	Classic ketogenic diet ratio 3:1 (40), ratio 4:1 (1), and modified ketogenic diet with medium-chain triglycerides (1)	21 (63.6%) ≥50% seizure reduction 14 (42.4%) ≥90% seizure reduction 9 (27.3%) seizure free	19 (79.2%) ≥50% seizure reduction 13 (54.2%) ≥90% seizure reduction 9 (37.5%) seizure free	16 (100%) ≥50% seizure reduction 11 (68.8%) ≥90% seizure reduction 10 (62.5%) seizure free	24 mo: 7 (100%) ≥50% seizure reduction 5 (71.4%) ≥90% seizure reduction 4 (57.1%) seizure free	33 (78.6%) on diet at 3 mo 24 (57.1%) on diet at 6 mo 16 (38%) on diet at 12 mo 7 (16.7%) on diet at 24 mo

Articles	Selection				Comparability	Outcome			Total Score (Out of 9)	Power
	Representativeness of the present cohort	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequate follow-up		
Pires ME, 2013	★		★	★	★	★	★	★	7	Good
Dressler A, 2015	★		★	★	★	★	★	★	7	Good
Ismayilova N, 2018	★		★	★	★	★	★	★	7	Good
Wirrell E, 2018	★		★	★	★	★	★	★	7	Good
Riantarini I, 2019	★		★	★	★	★	★	★	7	Good
Armeno M, 2021	★		★	★	★	★	★	★	7	Good
Liu Y, 2021	★	★	★	★	★	★	★	★	8	Good
Herrero JR, 2021	★		★	★	★	★	★	★	7	Good

Figure 2. Assessment of risk of bias on included studies using Newcastle-Ottawa Quality Assessment Form.

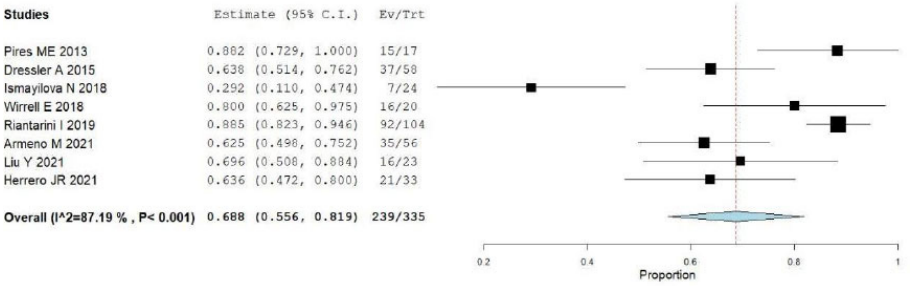

Figure 3. Forrest plot of ≥50% seizure reduction with ketogenic diet therapy in infants with epilepsy.

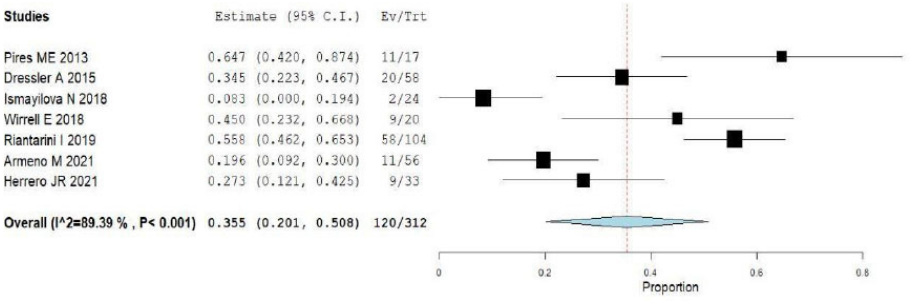

Figure 4. Forrest plot of seizure-free with ketogenic diet therapy in infants with epilepsy.

1. Non-compliance, n = 12/29 (41%)
2. Ineffectiveness, n = 41/87 (47%)
3. Adverse effects, n = 20/81 (25%): n = 5 GI disturbances; n = 2 "acidosis"; n = 2 "poor tolerability"; n = 2 "dehydration and acidosis", n = 1 "markedly elevated triglyceride level"; n = 1 "hypercalciuria and bone fracture"; n = 1 hypertransaminasemia
4. Severe infections, n=8/22 (36%)
5. Seizure-free, n = 9/40 (22%)
6. Death due to causes unrelated to diet, n = 17/87 (19%)
7. Poor oral intake, n=3/22 (14%)

Adverse Side Effects

The adverse side effects were assessed in five studies, which included a total of 355 infants. The most frequently reported adverse side effects were dyslipidemia (131/355, 36.9%), gastrointestinal disturbances (66/355, 18.6%), hyperketosis/acidosis (42/355, 11.8%), hypercalciuria (36/355, 10.1%), hypoglycemia (36/355, 10.1%), and nutritional deficiency (33/355, 9.3%).

DISCUSSION

In this meta-analysis, we investigated the efficacy of ketogenic diet therapy (KDT) in reducing seizure frequency in infants with epilepsy. Our findings indicate that KDT can be an effective treatment for reducing seizure frequency in infants with epilepsy. Approximately 69% of infants achieved a 50% or greater reduction in seizures after three months of receiving KDT, and 36% became seizure-free.

These findings are consistent with a previous systematic review from Lyons et al. that reported similar response rates in infants with epilepsy who received KDT. The review found that 59% of participants experienced a 50% or greater reduction in seizures, and 33% became seizure-free within three months of starting KDT.[19] These response rates appear comparable to those observed in older children and adolescents. A systematic review of uncontrolled studies from Lefevre et al. investigating the efficacy of KDT in children and adolescents with refractory epilepsy showed that 56% of participants experienced a 50% or greater reduction in seizures, with 16% becoming seizure-free.[20] Another review by Sourbron et al. investigated the efficacy and tolerability of KD and MAD in children and adolescents with refractory epilepsy. The participants were divided into two groups, an intervention group and a control group. The review reported that 35-56.1% of participants in the intervention group, receiving KDT or modified Atkins diet (MAD), achieved a 50% or greater seizure reduction compared to 6-18.2% in the control group. The efficacy of KDT was statistically significant compared to the control group: RR = 5.1 (95% CI 3.18-8.21, $p < 0.001$).[21]

Interestingly, higher response rates were observed in infants compared to older children, which may be attributed to better compliance in younger children. Riantarini et al. showed that Infants may have a higher level of dietary compliance due to simpler meal plans and greater control exerted by parents.[15] The mean age of infants starting KDT in our review was 8.64 months, and it has shown a significant efficacy (69%) in reducing seizure frequency. These results are supported by the findings of Ismayilova et al.[13], which

Table 3. Reported adverse effects in infants after receiving ketogenic diet therapy

Adverse side effect	Armeno et al[16] (n=56)	Dressler et al[12] (n=115)	Riantarini I et al[15] (n=115)	Ruiz-Herrero J et al[18] (n=42)	Wirrell et al[14] (n=27)	Total (n= 355 (%))
GI disturbances (vomiting, diarrhea, constipation)	32	-	19	9	6	66 (18.6%)
Nutritional deficiency (zinc, selenium, vit e, vit A, vit D, vit B12, carnitine)	18	15				33 (9.3%)
Hyperketosis/ acidosis	27		5	9	1	42 (11.8%)
Hypertriglyceridemia/ hypercholesterolemia	19	46	4	59	3	131 (36.9%)
Hypocalcemia	4					4 (1.1%)
Food refusal/ poor oral intake	7		5		1	13 (3.7%)
Nephrocalcinosis/lithiasis	2	4	2			8 (2.3%)
Hypercalciuria	8		10	18		36 (10.1%)
Low T3/TSH	2					2 (0.6%)
Hematological	8					8 (2.3%)
GERD	5					5 (1.4%)
Hypoglycemia	14	1	9	11	1	36 (10.1%)
Weight gain		2				2 (0.6%)
Growth deficit/ weight loss		6	1		1	8 (2.3%)
Infection			15			15 (4.2%)
Dehydration			2	4	1	7 (2.0%)
Lipoid pneumonia			1			1 (0.3%)
Hepatitis/ increased liver enzyme			1	16		17 (4.8%)
Pancreatitis			1			1 (0.3%)
GI bleeding			1			1 (0.3%)
Chorea/dystonia			1			1 (0.3%)
Allergic reaction/rash			1			1 (0.3%)
Metabolic encephalopathy			1			1 (0.3%)
Hyperuricemia				19		19 (5.4%)
Anorexia				1		1 (0.3%)

indicated a tendency for a better response to KDT in infants younger than 12 months (28%) compared to those older than 12 months (21%).[13]

Retention rates in infants receiving KDT in our review were similar to those reported in randomized controlled trials (RCTs) involving infants and older children. Retention rates ranged from 74% to 90% at 3-4 months, 66% at six months, and 58% at 16 months. Martin-McGill et al. presented that retention rates tended to be higher in children under two years old, likely due to parental control and management of their diet.[9]

The most common adverse effects reported in our review were dyslipidemia and gastrointestinal disturbances, including vomiting, diarrhea, and constipation. Dyslipidemia was observed in 36.9% of infants, which was higher than findings from other systematic reviews. Cai et al. conducted a study on the safety and tolerability of the ketogenic diet for treating refractory childhood epilepsy. In their research, hyperlipidemia occurred in 12.8% of older children. The most common adverse effect in older children was gastrointestinal disturbances, accounting for 40.6% of all cases.[22] In our review, gastrointestinal disturbances occurred in 18,6% of infants, lower than in older children. Similar to studies on older children, these adverse effects rarely led to diet discontinuation. Most of them were well tolerated and manageable with medications or dietary adjustments.[23] However, the specific time these adverse effects began was not reported. The timing of adverse effects associated with ketogenic diet therapy (KDT) is an important aspect that should be reported in future studies. Understanding the timing of side effects can help healthcare professionals anticipate and manage potential adverse events more effectively. By including data on the timing of side effects in studies on KDT, healthcare professionals can gain insights into when specific adverse effects may occur during treatment. This information can be valuable in clinical practice, allowing healthcare providers to inform patients and their families about potential side effects and provide appropriate support and intervention when needed.

This review has several limitations. All included studies were uncontrolled observational studies, and no randomized controlled trials were available for analysis. Additionally, factors such as concomitant use of antiepileptic drugs (AEDs), additional treatments or changes during KDT, additional diets, dose reduction, and reasons for diet discontinuation or adverse effects were not consistently detailed, which may have influenced the effectiveness of KDT. Further research is needed, particularly high-quality trials comparing KDT to placebo or combination therapy. Additionally, publication bias against negative results of KDT should be considered.

Our meta-analysis identified significant heterogeneity due to various factors, including seizure type, epilepsy syndrome, types of KDT, additional diets, and concomitant use of AEDs. Despite this heterogeneity, the findings remained statistically significant after applying the binary random effects model.

CONCLUSION

Our review suggests that ketogenic diet therapy (KDT) demonstrates potential as an effective and well-tolerated therapy for epilepsy in infants. However, well-conducted randomized controlled trials (RCTs) comparing KDT to a placebo or a combination of KDT and AED are needed to validate these findings further and strengthen the evidence base. Additionally, further analysis is necessary to control for confounding factors.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contribution

All authors designed the research. NAT, SM, and DC did the research. NAT and PA did the statistical analysis. NAT and SM wrote the first draft, and all authors contributed to writing the final report.

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