

Advances in Ketogenic Diet Therapies in Pediatric Epilepsy:

A Systematic Review

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Abstract

Objective: To review the effects of the ketogenic diet on epilepsy in children and adolescents.

Data Sources: A literature search was conducted in PubMed with no publication date or language restrictions based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Keywords used included *children, adolescent, ketogenic diet, epilepsy, and seizure*.

Study Selection: After excluding articles that did not meet the inclusion criteria,

such as missing variables of study, adult population, and nonrandomized clinical trials, a total of 12 studies were included in the final review.

Data Extraction: Data on study design, duration, sample size, population, and type of intervention were collected using a standard template.

Results: The ketogenic diet and its modified versions were noted to have beneficial effects in reduction of seizure frequency and severity, with manageable adverse effects such as gastrointestinal disturbances, dehydration, dyslipidemia,

hyperuricemia, infection, and metabolic acidosis.

Conclusions: Depending on patient compliance and comorbidities, all variations of the ketogenic diet were found to be helpful for seizure treatment, whether as an additive or an alternative treatment option, for children and adolescents with epilepsy.

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Epilepsy is a common neurological disorder affecting children and adolescents worldwide, with an annual incidence rate of 5–7 cases per 100,000 and a prevalence rate of 20–60 cases per 100,000.¹ Epilepsy is recurrent seizures with brief episodes of involuntary movements involving part of the body (partial) or all of the body (generalized) with or without loss of consciousness, bowel, and bladder function.² The major causes that lead to epilepsy are inherited disorders, congenital anomalies, fever, central nervous system infection, hydrocephalus, and brain tumors.³ Approximately 20%–40% of epilepsy cases are refractory or drug-resistant to standard antiepileptic drugs and require alternative treatment modalities including ketogenic diet therapy, surgical treatment, and vagal nerve stimulation.^{4,5}

The ketogenic diet refers to a dietary composition of high fat, low carbohydrate, and adequate protein, which

results in a ketogenic state of human metabolism and is considered to reduce seizure frequency.^{5–7} There are 4 major types of ketogenic diet therapy: the classic ketogenic diet (cKD), modified Atkins diet (MAD), medium-chain triglyceride ketogenic diet (MCTKD), and low-glycemic index treatment (LGIT).⁸ Reduced excitability of neurons as a result of multiple mechanisms in the brain and alteration of gut microflora plays a role in the positive effects of the ketogenic diet on epilepsy.⁹ The type of diet should be considered based on the patient's age, family conditions, and severity and type of epilepsy.¹⁰

Evidence for the ketogenic diet in epilepsy in previous studies is limited by small sample size, high attrition rates, lack of evidence in adults, and limited number of studies.^{6,7} Adverse effects associated with ketogenic diets such as gastrointestinal problems, weight loss, and

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Clinical Points

- Compared to conventional antiepileptic drug therapy with no dietary interventions, the ketogenic diet demonstrated favorable effects in the treatment of children and adolescents with epilepsy, particularly those with refractory epilepsy.
- The ketogenic diet displayed favorable safety profiles, with adverse events being generally manageable and outweighed by the potential benefits.
- Nonadherence to the ketogenic diet is a common issue, often stemming from challenges associated with tolerability and feasibility.

cardiovascular complications also remain a limiting factor in studies.^{6,7} In this review article, we aim to present the effects of the ketogenic diet on epilepsy in children and adolescents to provide a better understanding for clinicians and patients.

METHODS

A systematic search was conducted in PubMed with no publication date or language restrictions based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)¹¹ and followed a predefined protocol. The primary aim of the review was to evaluate the efficacy of the ketogenic diet in children and adolescents with epilepsy. Epilepsy was defined as recurrent seizures with brief episodes of involuntary movements of the whole body or body parts with or without loss of consciousness, bowel, and bladder function. We included all 4 major types of ketogenic diets (cKD, MAD, MCTKD, and LGIT) and defined ketogenic diet as a dietary composition of high fat, low carbohydrate, and adequate protein. Articles on various types of ketogenic diet as intervention and efficacy were selected. The secondary aim of the study was to highlight the possible adverse effects of various types of ketogenic diet.

Inclusion and Exclusion Criteria

Articles were included if (1) the study population included children and adolescents with epilepsy, (2) they implemented a ketogenic diet, and (3) they were randomized controlled trials (RCTs) exploring the efficacy of a ketogenic diet. Articles were excluded if (1) they included adults or noneligible patients (eg, autistic children and Angelman syndrome) as the study population, (2) they were not RCTs or were ongoing trials or non–full-text articles, (3) the intervention of interest was not a ketogenic diet, and (4) the outcome of interest was not efficacy.

Search Strategy and Selection

We followed PRISMA guidelines in conducting the systematic review exploring the efficacy of a ketogenic

diet. Articles in PubMed were searched using the search terms (("children"[Title/Abstract] OR "adolescent"[Title/Abstract] OR "toddler"[Title/Abstract] OR "newborn"[Title/Abstract] OR "infant"[Title/Abstract]) AND ("ketogenic diet"[Title/Abstract] OR "keto diet"[Title/Abstract] OR "atkins diet"[Title/Abstract] OR "low glycemic index treatment"[Title/Abstract] OR "classic ketogenic diet"[Title/Abstract] OR "medium chain triglyceride ketogenic diet"[Title/Abstract]) AND ("epilepsy"[Title/Abstract] OR "seizure"[Title/Abstract])) AND ((randomized controlled trial[Filter]) AND (fft[Filter]) AND (allchild[Filter])).

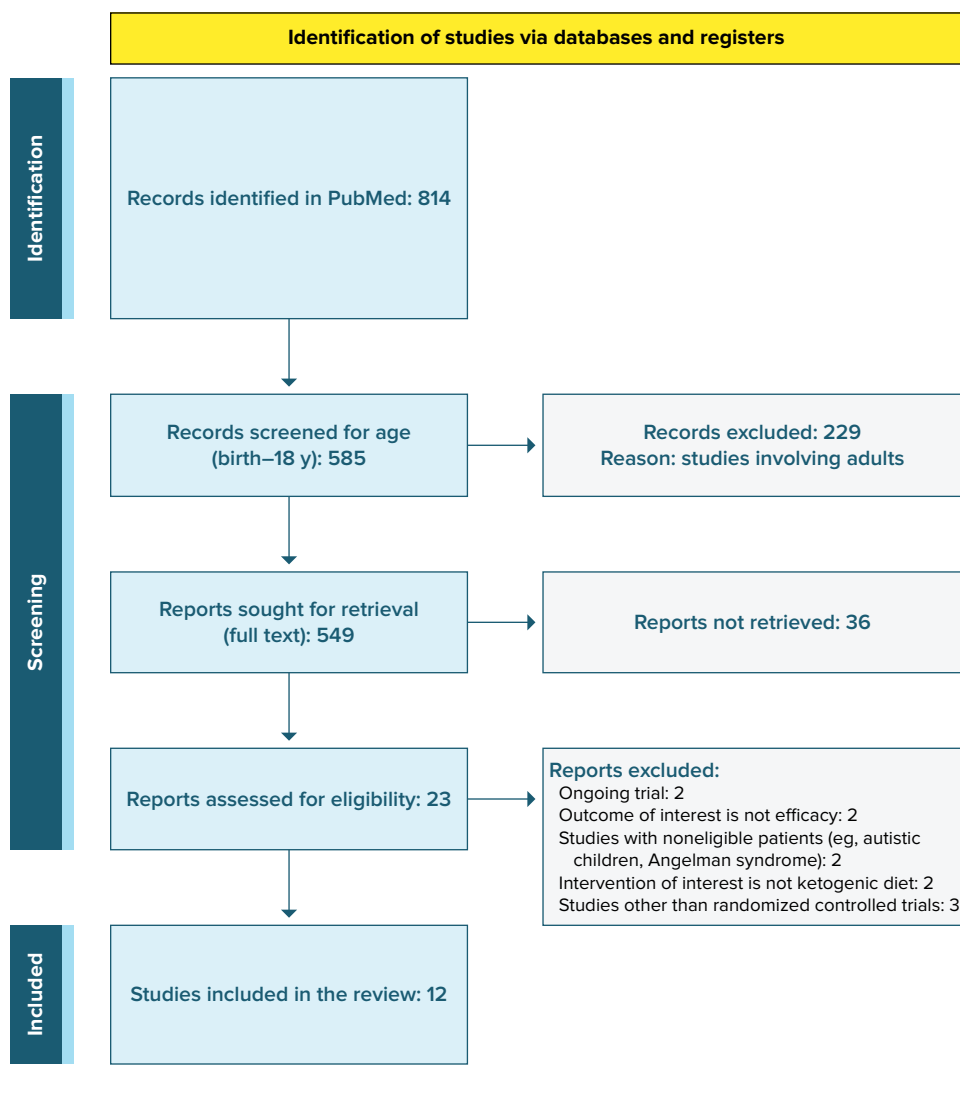
The title and abstract of articles retrieved from the initial search were evaluated. Full texts of included articles were assessed, and those that did not meet the inclusion criteria were discarded. Any disagreements were discussed and resolved by consensus and consultation with an expert. Data on study name (first author), study design, duration, sample size, population characteristics (country, mean/median age in years, and sex [%]), type of intervention (various types of ketogenic diet), and outcomes (efficacy and adverse effects) were collected using a standard template, and any disagreement was resolved by the authors (Y-C.H. and D.P.). Figure 1 describes the data collection process.

RESULTS

The search strategy resulted in 814 articles. A total of 12 articles were included in the final review. The RCTs were conducted in various countries including the United States, the Netherlands, the United Kingdom, Korea, and India. Table 1 provides the characteristics of the studies, and Table 2 describes the findings.

Several studies, including Lambrechts et al,¹² Neal et al,¹³ and de Kinderen et al,²⁰ compared the efficacy of the ketogenic diet with no dietary intervention for treating drug-resistant epilepsy in children and adolescents. Lambrechts et al¹² found that, at 4 months, the proportion of children with >90% and >50% seizure reduction was significantly higher in the ketogenic diet group compared to the no dietary intervention group (11.5% vs 4.5% and 27% vs 4.5%, respectively; $P = .070$). Similarly, Neal et al¹³ found that, at 3 months, the proportion of children with >90% and >50% seizure reduction was significantly higher in the ketogenic diet group compared to the no dietary intervention group (7% vs 0%, $P = .0582$ and 38% vs 6%, $P < .0001$, respectively). The study conducted by de Kinderen et al²⁰ also found that the proportion of children with >50% seizure reduction was higher in the ketogenic diet group compared to the no dietary intervention group (50% vs 18.2%). These studies indicate that the ketogenic diet is an effective therapy for reducing seizure frequency and severity when compared to no dietary intervention.

Figure 1.

Flow Diagram of the Systematic Review Study Selection

Lakshminarayanan et al,¹⁶ Sharma et al,¹⁷ and Sharma et al¹⁹ conducted studies comparing modified versions of the ketogenic diet with no dietary intervention for treating drug-resistant epilepsy in children and adolescents. These studies indicate that modified versions of the ketogenic diet are more effective in treating epilepsy in children and adolescents than no dietary intervention. Lakshminarayanan et al¹⁶ compared LGIT with no dietary intervention and found that at 3-month follow-up, the change in seizure frequency as compared to baseline was better in the LGIT group compared to the no intervention group (–15% [95% CI, –10% to –21%] vs 10% [95% CI, 6% to 15%], $P = .01$). Similarly, Sharma et al¹⁷ compared MAD with no dietary intervention, while Sharma and colleagues¹⁹ compared simplified MAD with no intervention. Both studies demonstrate that the proportion of children with >90%

seizure reduction (30% vs 7.7%, $P = .005$ and 9.5% vs 5%, $P = .09$, respectively) and >50% seizure reduction (52% vs 11.5%, $P < .001$ and 56.1% vs 7.5%, $P < .0001$, respectively) was significantly higher in the dietary intervention group compared to the control group.

Moreover, studies, such as that of Kim et al,¹⁴ Gupta et al,¹⁵ and Neal et al,¹⁸ compared 2 distinct types of ketogenic diet (cKD vs MAD, MAD vs LGIT, and cKD vs MCTKD, respectively) for treating drug-resistant epilepsy in children. These studies revealed comparable efficacy and tolerability of these dietary interventions.

Bergqvist et al²¹ found that gradual initiation of the ketogenic diet leads to greater seizure reduction and fewer adverse events compared to fasting initiation (at 3 months, >50% seizure reduction: 67% vs 58%, $P = .03$). On the other hand, Kossoff et al²² found no significant difference in seizure reduction between initial

Table 1.
Study Characteristics

Study	Country	Study design	Population	Sample size	Duration	Mean/median age, y	Female, %	Intervention	Outcomes
Lambrechts et al ¹²	The Netherlands	RCT	Children and adolescents aged 1–18 y with refractory epilepsy	48	July 2010–August 2014	KD: 7.8 CAU: 8.1	KD: 30.8 CAU: 59.1	KD vs CAU (26 vs 22)	<ul style="list-style-type: none">• >50% seizure reduction• Mean percentage of seizure severity• Side effects
Neal et al ¹³	United Kingdom	RCT	Children and adolescents aged 2–16 y with refractory epilepsy	145	December 2001–July 2006	Age group: 2–6 y 7–11 y 12–16 y (only proportion of children to each age group is given, no mean age)	KD: 48 CAU: 47	KD vs CAU (73 vs 72)	<ul style="list-style-type: none">• Reduction in seizure frequency• Tolerability
Kim et al ¹⁴	Korea	RCT	Children aged 1–18 y with refractory epilepsy	104	March 2011–March 2014	cKD: 4.9 ± 4.0 MAD: 4.8 ± 4.0	cKD: 37 MAD: 51	cKD vs MAD (51 vs 53)	At 3 and 6 mo after diet therapy <ul style="list-style-type: none">• >50% reduction in seizures• >90% reduction in seizures
Gupta et al ¹⁵	India	RCT	Children aged 6 mo to 14 y with drug-resistant epilepsy	60	February 2018–March 2019	MAD: 30 LGIT: 24		MAD vs LGIT (30 vs 30)	<ul style="list-style-type: none">• Complete cessation of seizure• >50% and 90% seizure frequency reduction
Lakshminarayanan et al ¹⁶	India	RCT	Children aged 2–8 y with refractory epilepsy	40	March 2011–July 2012	LGIT: 3.85 ± 1.98 CAU: 3.95 ± 1.31	27.5	LGIT vs CAU (20 vs 20)	<ul style="list-style-type: none">• Seizure frequency reduction• Seizure freedom• Diet compliance
Sharma et al ¹⁷	India	RCT	Children aged 2–14 y with refractory epilepsy	102	May 2009–March 2011	MAD: 4.7 ± 2.8 No dietary intervention: 5.2 ± 3.3	23.5	MAD vs no dietary intervention (50 vs 52)	<ul style="list-style-type: none">• >90% seizure reduction• >50% seizure reduction• Seizure freedom
Neal et al ¹⁸	United Kingdom	RCT	Children aged 2–16 y with refractory epilepsy	145	December 2001–July 2006	Age group: 2–6 y 7–11 y 12–16 y (only proportion of children to each age group is given, no mean age)	47.58	cKD vs MCTKD (73 vs 72)	<ul style="list-style-type: none">• Efficacy• Tolerability
Sharma et al ¹⁹	India	RCT	Children aged 2–14 y with refractory epilepsy	81	September 2012–November 2015	Simplified MAD: 5.6 ± 3.4 No dietary intervention: 4.8 ± 3	20.98	Simplified MAD vs no dietary intervention (41 vs 40)	<ul style="list-style-type: none">• >90% seizure reduction• >50% seizure reduction• Seizure freedom
de Kinderen et al ²⁰	The Netherlands	RCT	Children and adolescents aged 1–18 y with intractable epilepsy	48	August 2010–September 2014	KD: 7.8 CAU: 8.1	KD: 30.8 CAU: 59.1	KD vs CAU (26 vs 22)	<ul style="list-style-type: none">• >50% seizure reduction• Health care costs• Quality-adjusted life-years
Bergqvist et al ²¹	United States	RCT	Children aged 1–14 y with intractable epilepsy	48	...	5.3 ± 2.7	29	Fasting initiation KD vs gradual initiation KD (24 vs 24)	<ul style="list-style-type: none">• >50% seizure reduction• >90% seizure reduction• Seizure freedom
Kossoff et al ²²	United States	RCT	Children aged 3–18 y with refractory epilepsy	20		10 g: 7.5 20 g: 9.8	10 g: 40 20 g: 60	Initial 10 g vs 20 g of carbohydrate/d of MAD (10 vs 10)	<ul style="list-style-type: none">• >50% seizure reduction
Kang et al ²³	South Korea	RCT	Children aged 6–60 mo with intractable infantile spasm	35	2005–2008	Short-term KD: 1.15 Long-term KD: 1.25	Short-term KD: 31.2 Long-term KD: 36.8	Short-term KD (8 mo) vs long-term KD (>24 mo) (16 vs 19)	<ul style="list-style-type: none">• Median duration until seizure cessation• Relapse rate after discontinuation of KD

Abbreviations: CAU = care as usual, cKD = classic ketogenic diet, LGIT = low-glycemic index treatment, MAD = modified Atkins diet, MCTKD = medium-chain triglyceride ketogenic diet, RCT = randomized controlled trial.

Table 2.
Study Results

Study	Intervention	Seizure activity (outcome 1)	Seizure reduction (outcome 2)	Adverse event	Conclusion
Lambrechts et al ¹²	KD vs CAU (26 vs 22)	The mean seizure frequency at 4 mo compared to baseline was significantly lower in the KD group compared to the CAU group (56%, 95% CI, 36–76 vs 99%, 95% CI, 65%–133%, $P = .024$)	The proportion of children with >90% and >50% seizure reduction at 4 mo was significantly higher in the KD group compared to the CAU group (11.5% vs 4.5% and 27% vs 4.5% respectively, $P = .070$)	Gastrointestinal side effects	KD is an effective therapy compared to CAU, both with regard to seizure frequency and severity
Neal et al ¹³	KD vs CAU (73 vs 72)	The mean percentage of baseline seizures after 3 mo was significantly lower in the KD group compared to the control group (62% vs 136.9%, 95% CI, 42.4%–107.4%, $P < .0001$)	The proportion of children with >90% and >50% seizure reduction at 3 mo was significantly higher in the KD group compared to the CAU group (7% vs 0%, $P = .0582$ and 38% vs 6%, $P < .0001$, respectively)	Constipation (33%), vomiting (24%), lack of energy (24%), hunger (22%), and diarrhea (13%)	KD should be included in the management of children with drug-resistant epilepsy; however, possible side effects should be considered alongside the risk-benefit of other treatments
Kim et al ¹⁴	cKD vs MAD (51 vs 53)	After 3 and 6 mo, the KD group had a lower mean percentage of baseline seizures compared with the MAD group (38.6% vs 47.9% and 33.8% vs 44.6%, respectively), but the differences were not statistically significant (95% CI, 24.1–50.8, $P = .291$ for 3 mo and 95% CI, 17.8–46.1, $P = .255$ for 6 mo)	The proportion of children who had >50% and >90% reduction in seizure frequency was consistently higher in the cKD group compared to the MAD group. However, the differences in the proportion of patients with >50% and >90% seizure reduction were also not statistically significant between the 2 groups ($P = .527$ for >50%, $P = .314$ for >90%)	Gastrointestinal disturbances, lack of energy, dyslipidemia, hyperuricemia, infection, and metabolic acidosis	MAD had advantages with respect to better tolerability and fewer serious side effects, but cKD is more suitable as the first line of diet therapy in patients <2 y of age
Gupta et al ¹⁵	MAD vs LGIT (30 vs 30)	The proportion of children who achieved seizure freedom at 12 wk was comparable between the 2 groups ($P = .42$), and the chance of seizure freedom with MAD was better (relative risk reduction: –1.5, 95% CI, 10.9–0.5)	The number of children who had more than 90% seizure reduction was also similar between the groups ($P = .21$), but the proportion of children with 50%–90% seizure reduction was significantly higher in the LGIT group ($P = .03$) at 12 wk	The most common adverse effects were lethargy, constipation, and vomiting	Seizure freedom at 12 wk was comparable between MAD and LGIT for the treatment of drug-resistant epilepsy
Lakshminarayanan et al ¹⁶	LGIT vs CAU (20 vs 20)	At 3-mo follow-up, the change in seizure frequency compared to baseline was better in the intervention arm: –15%, 95% CI, –10% to –21% vs 10%, 95% CI, 6%–15%, $P = .01$	The number needed to treat for more than 50% seizure reduction was 3 and for more than 90% seizure reduction was 10 at 3-mo follow-up	Lethargy and vomiting	LGIT along with ongoing antiseizure medications is more efficacious than antiseizure medications alone
Sharma et al ¹⁷	MAD vs no dietary intervention (50 vs 52)	The mean seizure frequency at 3 mo compared to baseline was significantly less in the intervention group compared to the control group: 59%, 95% CI, 44–74.5 vs 95.5%, 95% CI, 82–109, $P = .003$	The proportion of children with >90% seizure reduction (30% vs 7.7%, $P = .005$) and >50% seizure reduction was significantly higher in the intervention group (52% vs 11.5%, $P < .001$) compared to the control group	Constipation (46%), anorexia (18%), vomiting (10%), and lethargy (6%)	MAD was found to be effective and well tolerated in children with drug-refractory epilepsy
Neal et al ¹⁸	cKD vs MCTKD (73 vs 72)	After 3, 6, and 12 mo, there were no statistically significant differences in mean percentage of baseline seizures between the 2 groups	After 3, 6, and 12 mo, there was no significant difference between the 2 groups in the numbers of children who had >90% or >50% seizure reduction	Constipation, vomiting, hunger, and taste problems were the main side effects of both diets	cKD and MCTKD were comparable in efficacy and tolerability

(continued)

Table 2 (continued).

Study	Intervention	Seizure activity (outcome 1)	Seizure reduction (outcome 2)	Adverse event	Conclusion
Sharma et al ¹⁹	Simplified MAD vs no dietary intervention (41 vs 40)	The mean seizure frequency at 3 mo compared to baseline was significantly less in the intervention group compared to the control group: 47.5%, 95% CI, 35.3–59.5 vs 118.9%, 95% CI, 94.1–143.8, $P < .0001$	The proportion of children with >90% seizure reduction (19.5% vs 5%, $P = .09$) and >50% seizure reduction was significantly higher in the intervention group (56.1% vs 7.5%, $P < .0001$) compared to the control group	Constipation (16.6%), weight loss (13.8%), anorexia (8.3%), and lethargy (8.3%)	A simplified version of MAD was found to be feasible, efficacious, and well tolerated
de Kinderen et al ²⁰	KD vs CAU (26 vs 22)	The proportion of children with >50% seizure reduction was higher in KD compared to CAU (50% vs 18.2%)	The mean costs per patient were €20,986 for KD compared to €15,245 for CAU	...	KD was effective in reducing seizure frequency; the study failed, however, to show improvements in QOL
Bergqvist et al ²¹	Fasting initiation KD vs gradual initiation KD (24 vs 24)	At 3 mo, the median percentage seizure reduction rate was 78% in fast initiation KD compared to 93% in gradual initiation KD ($P = .0002$)	At 3 mo, the proportion of children with >50% seizure reduction was 58% in the fasting initiation KD group compared to 67% in the gradual initiation KD group ($P = .03$)	Vomiting, dehydration, hypoglycemia, and weight loss	Gradual initiation KD results in fewer adverse events and is tolerated better overall while maintaining the efficacy of KD
Kossoff et al ²²	Initial 10 g vs 20 g of carbohydrate/d of MAD (10 vs 10)	>50% seizure reduction at 1 mo ($P = .33$), 3 mo ($P = .03$), and 6 mo ($P = .67$)	>90% seizure reduction at 1 mo ($P = .50$), 3 mo ($P = .10$), and 6 mo ($P = .50$)	Weight changes, constipation, and increased urine calcium to creatinine ratio	A starting carbohydrate limit of 10 g/d for children starting MAD may be ideal, with a planned increase to a more tolerable 20 g/d after 3 mo
Kang et al ²³	Short-term KD vs long-term KD (16 vs 19)	The median (\pm IQR) duration until achieving seizure-free outcomes after a trial of KD was 7.0 (\pm 28.7) d in the short-term KD group and 18.0 (\pm 33.0) d in the long-term KD group ($P = .3170$)	There was no statistically significant difference in relapse rate after discontinuation of KD in both groups (18.8% vs 15.8%, $P = 1.0000$)	Gastrointestinal discomforts, hypertriglyceridemia, hypercholesterolemia, hepatitis, and infectious disease (both groups) Osteopenia, ureteral stones, and significant growth failure (only in the long-term KD group)	Short-term use of KD in children who become spasm-free appears to be justified, with similar outcomes and recurrence rate and less growth disturbance compared to long-term KD

Abbreviations: CAU = care as usual, cKD = classic ketogenic diet, IQR = interquartile range, KD = ketogenic diet, LGIT = low-glycemic index treatment, MAD = modified Atkins diet, MCTKD = medium-chain triglyceride ketogenic diet, QOL = quality of life, RCT = randomized controlled trial.

10 g vs 20 g of carbohydrate/day for MAD. Similarly, Kang et al²³ compared short-term versus long-term ketogenic diet and observed comparable outcomes in both groups.

Adverse events were documented in various studies, and nonadherence to the ketogenic diet frequently arises due to challenges related to the diet's tolerability and feasibility. The most prevalent side effects associated with all forms of the ketogenic diet include gastrointestinal disturbances (such as constipation, vomiting, and diarrhea), lethargy, and weight loss. Other adverse effects encompass anorexia, taste abnormalities, dehydration, dyslipidemia, hyperuricemia, infection, and metabolic acidosis. In terms of tolerability, cKD and MCTKD exhibited similar outcomes.¹⁸ However, MAD displayed advantages by being better tolerated and presenting fewer severe side effects compared to cKD.¹⁴ Additionally, a study conducted by Bergqvist et al²¹ illustrated that gradually initiating the ketogenic diet resulted in fewer adverse events and overall better tolerability compared to

initiating the diet through fasting, while still maintaining the diet's efficacy.

DISCUSSION

In comparison with conventional antiepileptic drug therapy with no dietary interventions, the ketogenic diet has demonstrated favorable effects in the treatment of children and adolescents with epilepsy, particularly those with refractory epilepsy. In this population, the ketogenic diet appears to be capable of effectively controlling seizures. As a result of dietary interventions for 3–4 months, patients achieved significant decreases in baseline seizures, as well as notable reductions in seizures by >50% and >90%, and even seizure freedom. Often, achieving a seizure reduction of >50% is considered a clinically meaningful outcome, whereas achieving a reduction of >90% represents a substantial improvement in quality of life. The findings of this study indicate the potential for the ketogenic diet to improve

the lives of individuals with epilepsy. The ketogenic diet and its modified versions appear to have comparable efficacy. Patients' overall well-being and quality of life can greatly improve when they are seizure-free.

The current seizure management plan takes a multifaceted approach. Accurate diagnosis and evaluation, the use of appropriate antiepileptic drugs, implementation of lifestyle changes to reduce triggers and maintain overall health, and, for some people, consideration of alternative treatments like the ketogenic diet are all part of seizure management. The objective is to manage seizures while reducing adverse effects and increasing quality of life. The treatment plan is periodically assessed and modified as necessary.

Lambrechts et al¹² found that ketogenic diet therapy was an effective therapy compared to no dietary intervention regarding seizure frequency and severity. Neal et al¹³ suggested that ketogenic diet therapy should be considered as part of the management plan for children with drug-resistant epilepsy. However, the potential side effects of ketogenic diet therapy such as constipation (33%), vomiting (24%), lack of energy (24%), hunger (22%), and diarrhea (13%) should be carefully considered alongside the risk-benefit of other treatments. A variety of ketogenic diets are available to manage epilepsy, including Atkins, keto, classic, LGIT, and MCT. Keto emphasizes high fats, moderate proteins, and low carbs, while Atkins allows higher protein and carb intake. Traditional ketogenic diets are high in fat and low in carbohydrates and have adequate protein levels. LGIT restricts carbs with low-glycemic index. MCT incorporates MCT oil for higher carbohydrate and protein intake. Kim et al¹⁴ concluded that MAD had advantages with respect to better tolerability and fewer serious side effects, but cKD is more suitable as the first line of diet therapy in patients under 2 years of age. Additionally, Gupta et al¹⁵ found that the proportion of children achieving seizure freedom at 12 weeks was similar between the MAD and LGIT groups.

Lakshminarayanan et al¹⁶ demonstrated the superior efficacy of LGIT when used in conjunction with ongoing antiseizure medications, compared to antiseizure medication alone. LGIT versus no dietary intervention showed that the number needed to treat for more than 50% seizure reduction was 3 and for more than 90% seizure reduction was 10 at 3-month follow-up. In another study, Sharma et al¹⁷ found that MAD was effective and well tolerated in children with drug-refractory epilepsy, surpassing the outcomes of conventional antiepileptic drug therapy. The study demonstrated that the proportion of children with >90% seizure reduction (30% vs 7.7%, $P = .005$) and >50% seizure reduction (52% vs 11.5%, $P < .001$) was significantly higher in the intervention group compared to the control group. Neal et al¹⁸ found that cKD and MCTKD exhibited comparable efficacy and tolerability, and there were no statistically significant

differences in mean percentage of baseline seizures between the 2 groups or in seizure frequency reduction. Furthermore, Sharma et al¹⁸ demonstrated the feasibility, efficacy, and good tolerability of a simplified version of MAD and found that the proportion of children with >90% seizure reduction (9.5% vs 5%, $P = .09$, respectively) and >50% seizure reduction (56.1% vs 7.5%, $P < .0001$, respectively) was significantly higher in the intervention group compared to the control group.

de Kinderen et al²⁰ conducted a study that revealed the effectiveness of the ketogenic diet in reducing seizure frequency; however, there were no significant improvements in the quality of life of the participants. On the other hand, Bergqvist et al²¹ found that gradually initiating (starting ketogenic diet protocol with 1:1 ratio of fat: carbohydrate + protein by weight, full-calorie-goal meals, and then daily advanced to a 2:1, 3:1, and finally to a 4:1 ratio) the ketogenic diet resulted in fewer adverse events and better overall tolerability, while maintaining the diet's efficacy. Kossoff et al²² found that for children starting MAD, beginning with a carbohydrate limit of 10 g/day and gradually increasing it to a more tolerable 20 g/day after 3 months may be an optimal approach. Kang et al²³ demonstrated that short-term use of the ketogenic diet in children who become spasm-free appears to be justified, with similar outcomes, recurrence rate, and less growth disturbance compared to long-term use.

Overall, the ketogenic diet stands as a viable and efficacious alternative treatment option for children and adolescents with epilepsy. Moreover, the ketogenic diet has displayed favorable safety profiles, with adverse events being generally manageable and outweighed by the potential benefits.

Strengths and Limitations

The strengths of the current review include the comprehensive integration of evidence from 5 countries across 3 continents, alongside the meticulous adherence to the PRISMA protocol to evaluate evidence quality. Only RCTs were included, which adds to the strength in the level of evidence.

This review possesses certain limitations that should be acknowledged. First, the inclusion of only RCTs may have limited its comprehensiveness. Second, the available evidence regarding the efficacy of ketogenic dietary therapy for epilepsy is constrained by small sample sizes, high attrition rates, lack of evidence in adults, and the presence of adverse effects associated with ketogenic diet therapy, including gastrointestinal issues, weight loss, and lethargy.

CONCLUSION

In conclusion, the ketogenic diet represents a compelling and effective alternative treatment modality

for children and adolescents suffering from epilepsy. Its ability to significantly alleviate seizures, coupled with its generally acceptable safety profile, positions it as a valuable supplemental part of the treatment regimen in the management of pediatric epilepsy. Nonadherence to the ketogenic diet is a common issue, often stemming from challenges associated with the tolerability and feasibility, but continued research and improvements in the implementation and monitoring of the diet hold the potential for even greater success in the future.

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