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A Systemic Review

Effectiveness of a Ketogenic Diet in Children with Refractory Epilepsy: A Systemic Review

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ABSTRACT

A notable proportion (10%-20%) of children with epilepsy remain unresponsive to pharmacological treatment. Current strategies for the management of refractory epilepsy encompass surgical treatments (vagus nerve stimulation) as well as the adoption of a Ketogenic Diet. By adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, we conducted a systematic review to identify all relevant studies in English language that investigated the effectiveness of a Ketogenic diet in children with refractory epilepsy. A total of 125 studies were identified and eight, involving a total of 1330 patients, met the criteria. Of the identified eight studies, one was randomized controlled trial, one was systematic review/meta-analysis, and the rest were observational studies. More than half (54%) of the participants reported seizure resolution, while 17% became seizure-free after one month of initiating the ketogenic diet. Ketogenic diet have been shown to be efficacious for the treatment of epilepsy in infants.

INTRODUCTION AND BACKGROUND

Epilepsy is characterized by the occurrence of recurring epileptic seizures or alterations in behaviour and movement. These manifestations are directly caused by a basic disruption in the brain's electrical activity [1]. Epilepsy accounts for a substantial proportion of the global disease burden, impacting around 50 million individuals across the globe. The incidence of epilepsy shows a bimodal age distribution. It tends to be higher among individuals in the youngest and oldest age brackets [2]. In the United States, for instance, the estimated annual incidence rate is 86 per 100,000 in infants, gradually declining to approximately 23-31 per 100,000 in individuals aged 30 to 59 years. However, there is a subsequent increase in incidence rates beyond this age group, reaching 180 per 100,000 among those aged 85 and above [3].

In their lifespan, around 65% of patients diagnosed with epilepsy will experience seizure control through the use of antiepileptic medicines or achieve spontaneous remission [4]. Nevertheless, 10-20% of children remain unresponsive to pharmacological treatment. The existing approaches for managing refractory epilepsy include surgical interventions, such as vagus nerve stimulation, and the implementation of a Ketogenic Diet [5].

The process of ketogenesis, which involves the synthesis of ketone bodies, is largely observed in the liver. This process happens through the conversion of acetyl-CoA obtained from the breakdown of fatty acids via β-oxidation. The resulting ketone bodies are then transferred to extrahepatic tissues, where they undergo terminal oxidation. The ketone bodies play significant roles in various essential metabolic pathways, including fatty acid β-oxidation, gluconeogenesis, the tricarboxylic acid cycle, de novo lipogenesis, and sterol biosynthesis [6,7,8]. This metabolic process offers an alternate means of obtaining energy, particularly when an individual is in a fasting condition. In such a state, the supply of carbohydrates is restricted, while the availability of fatty acids is heightened. Consequently, this process serves as the primary source of energy [9]. Ketone bodies, namely β-hydroxybutyrate (BHB), have traditionally been recognised as an alternative energy source [7,10,11]. In humans, the metabolism of ketone bodies serves as a substantial fuel supply for the brain when carbohydrate intake is limited. Brain cells have the capacity to derive energy from both glucose and ketones, thereby exhibiting metabolic flexibility. In instances of significantly reduced carbohydrate consumption, beta-hydroxybutyrate (BHB) serves as the principal energy substrate for neurons [12].

The therapeutic use of fasting as a treatment for epilepsy was documented in the Hippocratic collection [13]. Following a two-year clinical study, the ketogenic diet was introduced in 1924 [14]. However, in the year 1921, Woodyatt and colleagues made an observation regarding the presence of ketones, namely acetone and β-hydroxybutyric acid, in individuals who were either experiencing hunger or following a diet that was high in fat and extremely low in carbohydrates [15]. In the same year, a Mayo Clinic physician published a case series on the implementation of a ketone-producing diet for patients with epilepsy [16]. During the 1920s and 1930s, the diet was extensively employed as a therapeutic approach for epilepsy. However, its utilisation experienced a notable decline subsequent to the emergence of novel and more efficacious antiseizure medications [13]. The newly developed antiseizure medications had a reduced incidence of adverse effects compared to their predecessors and showed enhanced compliance relative to a stringent dietary regimen. The

ketogenic diet saw a resurgence in the 1990s due to the dissemination of positive research findings. Additionally, the establishment of the Charlie Foundation, a non-profit organisation dedicated to disseminating knowledge on dietary therapies for individuals with epilepsy, can be attributed to the successful treatment of a 2-year-old child's epilepsy through the implementation of this therapeutic approach [17].

The classic ketogenic diet typically includes long-chain triglycerides and is commonly provided in a ratio of 4:1 or 3:1 of fats to non-fats (proteins and carbohydrates). At present, clinical practice involves the utilisation of four primary ketogenic diets: the conventional ketogenic diet, the medium-chain triglyceride (MCT) diet, the modified Atkins diet (MAD), and the low glycemic index therapy (LGIT). [18].

The objective of this review is to critically examine the existing body of evidence pertaining to the utilization and effect of a ketogenic diet as a therapeutic intervention for refractory epilepsy in paediatric patients.

METHODOLOGY

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 criteria were utilised to structure and present the results of this systematic literature review. [19].

Search Strategy

A Systematic review using the PRISMA 2020 guidelines was carried out in 30th October 2023. The following databases are used: PubMed, Google Scholar, ScienceDirect, and Research Gate with MeSH (Medical subject heading): ketogenic diet OR ("Diet, Ketogenic/adverse effects"[Majr] OR "Diet, Ketogenic/methods"[Majr] OR "Diet, Ketogenic/pharmacology"[Majr] OR "Diet, Ketogenic/statistics and numerical data"[Majr] OR "Diet, Ketogenic/therapeutic use"[Majr] OR "Diet, Ketogenic/therapy"[Majr]) AND Refractory epilepsy OR ("Drug Resistant Epilepsy/anatomy and histology"[Majr] OR "Drug Resistant Epilepsy/blood"[Majr] OR "Drug Resistant Epilepsy/diet therapy"[Majr] OR "Drug Resistant Epilepsy/ethnology"[Majr] OR "Drug Resistant Epilepsy/genetics"[Majr] OR "Drug Resistant Epilepsy/metabolism"[Majr] OR "Drug Resistant Epilepsy/pathology"[Majr] OR "Drug Resistant Epilepsy/physiology"[Majr] OR "Drug Resistant Epilepsy/statistics and numerical data"[Majr])

Inclusion and Exclusion Criteria

The research paper involving only human participants i.e. children >12 years, with refractory epilepsy, available for free full text and conducted within 10 years were included in this review. We restricted our choice of studies to exclude the following: Animal participants, studies published before 2012, patients aged more than 12 years, translated and other language studies, paid articles, and grey literature. Our selection of studies was limited to meta-analyses, systematic reviews, clinical trials, and prospective and retrospective observational cohorts. The fundamental foundation for our qualifying criteria was based on the population, intervention, comparison, and outcomes (PICO) criteria seen in Table 1.

Table 1: Study inclusion criteria

P (Population)	*Sex*	*Male and female*
	Race	*All*
	Refractory Epilepsy	Refractory epilepsy was defined as failure of seizure control despite use of two or more antiepileptic medications.
I (Intervention)	*Ketogenic Diet*	Classic ketogenic diet and alternate ketogenic diet
C (Comparison)	*1. With controls* *2. Pre-post study* *3. Different types of KDs*	The comparison group is either a control group which is not consuming ketogenic diet, pre- and post -intervention comparison of study population, and comparison of different types of KD.
O (Outcome)	*Seizure resolution*	Seizure resolution was defined as achieving ≥50% seizure reduction after ≥1 month of follow-up.
	Seizure freedom	100% seizure reduction after ≥1 month of follow-up.
	Adverse events	Any acute or chronic side effect observed with ketogenic diet

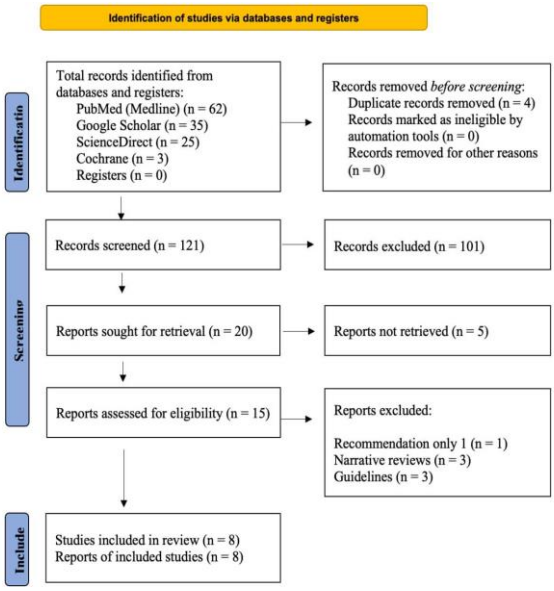
Selection of studies and data extraction

Two reviewers independently screened titles and abstracts and resolved any conflicts through consensus. If a disagreement persisted, a third reviewer would step in to mediate. All potentially relevant records were assessed by the same set of reviewers. The reasons for excluding studies from this review were meticulously documented. The initial review included observational studies, randomized controlled trials and systematic reviews/meta-analyses written in the English language that reported the effectiveness, efficacy and/or observed the possible adverse events after using the classic or alternative Ketogenic Diet to treat children with refractory epilepsy aged 0-12 years.

Search Strategy

A total of 125 publications were identified. After the elimination of four duplicate records, a total of 121 studies were subjected to screening and assessment to determine their eligibility based on the inclusion and exclusion criteria used in this review. Ultimately, only 20 research were found to meet the predetermined inclusion criteria. Five studies were removed from the analysis because the reports could not be retrieved. Seven were excluded as they included recommendations and recent updates on the topic. A total of eight studies were incorporated into the quality assessment and in the final analysis. A flowchart depicting the selection process under PRISMA guidelines, along with explanations for the exclusion of articles, is presented in Figure 1 below.

Figure 1: Flowchart of study selection process.



Quality assessment

In this review, the studies underwent quality evaluation by two different authors, each employing study-specific techniques. Each assessment tool utilized had its own scoring system. Out of the 8 papers examined, the quality assessment of these investigations and the corresponding tools are summarized in Table 2, Table 3, and Table 4. The evaluation process encompassed an assessment of potential bias in each study. For clinical trials, the revised Cochrane risk of bias 2 (RoB 2) tool was employed. The quality of observational studies was appraised using the adapted Newcastle Ottawa Scale. Systematic reviews and meta-analyses were subjected to evaluation using the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool.

The randomized controlled trial was scrutinized for potential biases using the latest Cochrane RoB 2 tool, which considers five specific risks of bias. Each risk of bias was assigned a score denoting whether it was low, high, or moderate. Consequently, the overall risk of bias for the trial was reported as either low, high, or moderate. The findings from the assessment using the revised Cochrane RoB 2 tool are presented in Table 2.

Table 2: Assessment of clinical trials using the revised Cochrane risk of bias 2 tool

First Author	Random allocation	Intervention non-adherence	Incomplete results	Inadequate assessment of the outcomes	Selective reporting	Final RoB judgement
El-Shafie AM et al. (2023) [20]	Low Risk	Low Risk	Low Risk	Moderate Risk	Low Risk	Moderate Risk

Similarly, the quality assessment of observational studies was conducted using the Newcastle Ottawa Scale (NOS). The evaluation involved scoring the studies with regard to the selection criteria applied to the study population, the comparison made, and the results reported. The final scores were categorized as either representing good, fair, or poor quality. A summary of the NOS assessments for the included observational studies can be found in Table 3.

Table 3: Newcastle Ottawa Scale adapted for observational studies [Hegzog]

First author	Selection				Comparability	Outcome		Final Result
	Representativeness of the sample	Sample size	Non-responders	Ascertainment of exposure	Based on design and analysis	Assessment of outcome	Statistical test	
Ruiz-Herrero J et al. (2021) [21]			+	+	++	++	+	7
Yang R et al. (2021) [22]	+	+	+	+	++	++	+	9
Israel RA et al. (2020) [23]			+	+	++	++	+	7
Rebollo MJ et al. (2020) [24]			+	+	++	++	+	7
Gurbuz G et al. (2019) [25]			+	+	++	++	+	7
Ismayilova N et al. (2018) [26]			+	+	++	++	+	7

Ref: Very Good Studies: 9-10 points, Good studies: 7-8 points, Satisfactory studies: 5-6 points, Unsatisfactory studies: 0-4 points

Finally, the assessment of systematic reviews and meta-analyses was performed by applying the AMSTAR 2 tool, which involves the consideration of 16 specific questions. The overall quality of these comprehensive studies was evaluated and categorized as either critically low, low, moderate, or high. The outcomes of the AMSTAR 2 tool assessment are presented in Table 4.

Outcomes:

The primary outcome was effectiveness of ketogenic diet therapy for epilepsy in children aged up to 12 years, presented as the number or proportion of children achieving ≥50% seizure reduction after ≥1 month of follow-up.
Secondary outcomes were:
1. Seizure free rates at ≥1 month of follow-up
2. KDT Retention rates
3. Side effects
Data extraction:
The following data (where available), were extracted for each study:
1. Study design
2. Number of children started on diet
3. Type of ketogenic diet
4. Seizure outcome at 1, 3, 6, 12, and 24 months
5. Seizure outcome at other recorded time points
6. Number of children remaining on diet at each time point
7. Adverse side effects in children

Data analysis:

Descriptive analysis was undertaken for the primary outcome and for seizure-free rates; data were presented as aggregate rates, ranges, median, and interquartile range (IQR), for numerical outcomes. Collective means were derived by aggregating study means or individual patient data, whenever available. The calculation of the collective standard deviation was not feasible due to the unavailability of data for all

studies. Narrative syntheses of retention rates, side effects, and diet-initiation methods were compiled. The results obtained from this analysis are presented in Table 4.

Table 4: Summary of the Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) tool

First author (Year)	Lyons et al. (2020) [27]
(1) PICO framework included	No
(2) Pre- defined methods and research proposal	Yes
(3) Design of study outlined	Yes
(4) Thorough literature search	Yes
(5) Selection of studies by two individuals	Yes
(6) Extraction of data by two individuals	Yes
(7) Record and reasons of reports excluded	Yes
(8) Detailed description of included studies	Yes
(9) Adequate RoB procedure followed	Yes
(10) Disclosure of funding sources	Yes
(11) Appropriate statistical analysis	Yes
(12) Effect of RoB of primary studies on meta- analysis result	Yes
(13) RoB considered in primary studies	Yes
(14) Investigation of heterogeneity	Yes
(15) Small study bias	No
(16) Potential conflicts reported	Yes
Total score (/16)	14
Final quality appraisal of the review	MODERATE
PICO: Population Intervention Comparison Outcome; RoB: risk of bias	

RESULTS

Study characteristics

A total of eight studies were included in the present review. Out of eight studies, two studies were conducted in the United Kingdom, one each in Egypt, Spain, China, Mexico, Chile, and Turkey. Of the included studies, one was a randomized controlled trial, one was a systematic review/meta-analysis, and the rest were observational studies. All the studies included seizures of heterogeneous aetiology. Overall sample size of the eight studies was 1330. The median age at the initiation of ketogenic diet therapy ranged from 7.7 months to 4.4 years. The males and females in this review were in similar proportions (50.7% vs 49.3%). The results obtained from this analysis are presented in Table 5.

Table 5: Details of the studies comprised in the review

Author (year)	Country	Study design	Sample size	Age at KD initiation (Maximum age and median/mean)	M/F (%)	Conclusion
El-Shafie AM et al. [20]	Egypt	RCT	40	4m-12y 4y	43.3/56.7	Classic KD (60%) and MAD KD (53.3%) is safe and effective therapy for the management of Drug Resistance Epilepsy with a positive impact on growth and EEG
Ruiz-Herrero J et al. [21]	Spain	Retrospective, study	42	2y 7.7m	50/50	KDT are useful and effective treatments in infancy. Mild side effects in 50% patients.
Yang R et al. [22]	China	Retrospective study	634	10y 2.6y	63.4/36.6	Optimal long-term management of ketogenic diet therapy has been shown to greatly enhance the rate of ketogenic diet retention, effectiveness, and infrequency of adverse effects.
Israel RA et al. [23]	Mexico	Case series	10	5y 3.5y	50/50	KD is a viable option for treating refractory epilepsy in children after at least 6 months following initiation.
Rebollo MJ et al. [24]	Chile	Retrospective study	35	7y 4.8y	45.7/54.3	KD is an effective therapy for paediatric patients with DRE without any nutritional consequences and easily controlled adverse events.
Lyons et al. [27]	UK	Systematic review	534	2y 13m	58/42	KD is a safe, acceptable, and effective treatment option for infants suffering from DRE.
Gurbuz G et al. [25]	Turkey	Retrospective study	6	9y 3y	33.3/66.7	A minimum of 50% reduction in seizure frequency was attained in 50% of affected patients with no life-threatening complications.
Ismayilova N et al. [26]	UK	Retrospective study	29	2y 1y	62/38	KD is well tolerated in newborns with severe epilepsies with roughly 50% improvement in seizure frequency/ severity without any negative impact on developmental course.

Ketogenic diet resulted in a reduction in the use of AEDs, Before the initiation of ketogenic diet, the majority of the children (57.5%) were on four or more AEDs, which reduced to 6.2% post-therapy. Similarly, the proportion of participants who were on 3 AEDs (40.8%) reduced to 16.2% post-therapy. Whereas, there was an increase in the proportion of participants using fewer AEDs, such as participants who were on 2 AEDs (18.2%) increased to 30.4% post-therapy and participants who were on single AED (12%) increased to 16.2% post therapy. The mean follow-up duration in this review was 18.3 months, which ranged from 8 months to 24 months. The mean three-months

retention rate was 80.4%, while with subsequent follow-up the retention rate reduced further, such as 53.0% at the end of 6 months, 53.8% at the end of 12 months, and 28% at the end of 24 months. The results obtained from this analysis are presented in Table 6.

Table 6: Number of anti-epileptic drugs, retention rate and follow up duration

Author (year)	Number of AED used at before KD	Number of AED used after KD	Retention rate	Follow-up duration (m)
El-Shafie AM et al. [20]	33.3% on 4 AED 53.3% on 3 AED 13.3% on 2 AED	Withdraw 1 AED in 26.7% 2 AED in 13.3%	1 month, 92.5% 3 months, 85%	24
Ruiz-Herrero J et al. [21]	31% on 4 AED 31% on 3 AED 31% on 2 AED 7% on 1 AED	3 months 2.4% on 4 AED 26% on 3 AED 33% on 2 AED 12% on 1 AED	3 months, 79% 6 months, 57% 12 months, 38% 24 months, 17%	24
Yang R et al. [22]	50% on ≥4 AED	—	3 months, 82% 6 months, 60.6% 12 months, 34.1%	12
Israel RA et al. [23]	100% on ≥4 AED	—	12 months 100%	12
Rebollo MJ et al. [24]	5.7% on ≥5 AED 80% on 3-4 AED 14.3% on <2 AED	—	3 months, 72% 24 months, 40%	24
Lyons et al. [27]	Mean, 2.9	—	3 months, 84% 6 months, 68% 12 months, 43% 24 months, 27%	24
Gurbuz G et al. [25]	100% on ≥4 AED	—	50%	8
Ismayilova N et al. [26]	31% on 4 AED 38% on 3 AED 14% on 2 AED 17% on 1 AED	10% on 4 AED 28% on 3 AED 45% on 2 AED 10% on 1 AED	1 month, 86% 6 months, 34.5%	18

AED: Anti-Epileptic Drugs, KD: Ketogenic Diet

The majority of the participants started on the Classic ketogenic diet, with more than half (55.6%) of the participants on the classic 3:1 ketogenic diet, while around one-third (34.2%) were on the classic 4:1 ketogenic diet. The modified Atkin Diet was introduced in 23.9% of the participants. Five out of 8 studies reported a non-fasting state during the initiation of a ketogenic diet. Resolution of seizure, which was assessed by ≥50% reduction in seizure frequency, was observed at different follow-up intervals. After one month, 54% of the participants reported seizure resolution, after three months of ketogenic diet 58% of the participants had seizure resolution. Similarly, after six, twelve and twenty-four months, 46.8%, 56.1% and 41.5% of the participants developed seizure resolution, respectively. Considering seizure freedom, after one, three, six, twelve and twenty-four months, 17%, 25.7%, 33.3%, 21.3% and 18.8% of the participants became seizure-free, respectively. The results obtained from this analysis are presented in Table 7.

Table 7: Effectiveness and types of KD

Author (year)	KD type ratio, (%)	Fasting	Common symptoms before the initiation of KD	Resolution of seizures (≥50% seizure reduction) with respective p-values	Seizure free
El-Shafie AM et al. [20]	Classic 4:1, 50% MAD, 50%	No	Myoclonic seizure (33.3%), infantile spasm (20%)	*After 3 months*, Classic, 46.7% ($p<0.05$) MAD, 73.3% ($p>0.05$) *After 6 months*, Classic, 40% ($P < 0.0001$) MAD, 53.3% ($P < 0.0001$)	*After 3 months*, Classic, 53.3% MAD, 26.7% *At 6 months*, Classic, 60% MAD, 46.67%
Ruiz-Herrero J et al. [21]	Classic 3:1, 95% Classic 4:1, 2.5% MAD, 2.5%	No	Etiological classification, predominantly structural causes.	*After 3 months*, 50% *After 6 months*, 45% *After 12 months*, 38% *After 24 months*, 17% (p-value not reported)	*After 3 months, 21.4%* *After 6 months, 21.4%* *After 12 months, 23.8%* *After 24 months, 9.5%*
Yang R et al. [22]	Classic 4:1, 2:1	Yes	Etiological classification, predominantly West syndrome (40.7%)	*After 3 months*, 55.5% ($p<0.001$), *After 6 months, 48.2%* ($p<0.001$); *After 12 months, 31.5%* ($p<0.001$)	*After 3 months, 26.2%* *After 6 months, 23.7%* *After 12 months, 19.2%*
Israel RA et al. [23]	Classic 3:1, 70% Classic 4:1, 20% Classic 2:1, 10%	—	Predominantly Tonic spasm, generalised and myoclonic seizures	*After 1 month*, 60% ($p<0.006$) *After 3 months*, 80% ($p<0.006$) *After 12 months*, 100% ($p<0.006$)	*After 1 month, 10%* *After 3 months, 20%* *After 12 months, 20%*
Rebollo MJ et al. [24]	Classic 4:1, 35% Classic 3:1, 14% MAD, 37% LGIT, 14%	No	Classified based on number of seizures per day: < 5 to status epilepticus. 5-10 seizures per day was predominated	*After 3 months*, 82.8% ($p=<0.0001$)	*After 3 months*, 20% ($p=<0.0001$)
Lyons et al. [27]	Classic 3:1-4:1, 88% MAD, 6%	40%	Infantile spasm>generalised seizures	*After 1 months*, 52% *After 3 months*, 60% *After 6 months*, 59% *After 12 months*, 55% *After 24 months*, 66%	*After 1 months*, 24% *After 3 months*, 23% *After 6 months*, 28% *After 12 months*, 22% *After 24 months*, 28%
				Overall, ≥ 50% seizure reduction in 58% population [prevalence 0.58 (0.52-0.64)]	
Gurbuz G et al. [25]	Classic 3:1, 33.3% Classic 4:1, 66.7%	No	Generalised status epilepticus (60%), focal seizures (40%)	*After 1 months*, 50% (p-value not shown)	*After 1 months*, 16.7%
Ismayilova N et al. [26]	Classic 3:1, 65.5% Classic 4:1, 31.1% MCT, 3.4%	No	Etiological classification, genetic cause predominated,	*After 3 months*, 31% (significant difference)	*After 3 months*, 6.9%

KD: Ketogenic Diet, MAD: Modified Atkins Diet, MCT: Medium Chain Triglyceride, LGIT: Low Glycemic Index Treatment

The majority of the studies frequently reported gastrointestinal side effects, the most common being in the form of gastrointestinal disturbances (35.8%), GERD (33.7%), constipation (30.7%), vomiting (17.1%), Diarrhea (15%) and less commonly pain abdomen (3.2%) and loss of appetite (3%). Dyslipidemia was developed in 19.6% of the study participants. Hypoglycemia was present in 15.8%. Other biochemical abnormalities reported were acidosis, and disturbances in calcium metabolism. Renal stones were also reported in three out of eight studies. Weight loss (33.3%), weight gain (40%) and behavioral problems (2%) were reported by one each study. The results obtained from this analysis are presented in Table 8.

Author (year)	GI side effects	Biochemical	Genitourinary	Others
El-Shafie AM et al. [20]	Constipation 33.3% Diarrhea 16.7% Vomiting 13.4%	—	—	—
Ruiz-Herrero J et al. [21]	GI disturbance 9.5%	Dyslipidemia 4.8% Hypoglycemia 21.4% Hypercalciuria 4.8%	Hyperuricemia 2.4%	—
Yang R et al. [22]	Constipation 24.9% Vomiting 15.8% Diarrhea 13.2% Abdominal pain 3.2%	Dyslipidemia 1.9% Acidosis 0.3% Hypoglycemia 0.3% Hypocalcemia 0.9%	Hyperuricemia 0.6% Renal stones 0.3%	—
Israel RA et al. [23]	Constipation 60% GERD 30%	Dyslipidemia 50%	Renal stone 10% UTI 20%	Weight gain 40%
Rebollo MJ et al. [24]	GI disturbances 62% Constipation 31.4	Dyslipidemia 14%	—	—
Lyons et al. [27]	Vomiting 6% Constipation 4% GERD 4% Loss of appetite 3%	Dyslipidemia 12% Acidosis 2%	Renal stones 3% Hematuria 2%	Behavioral problem 2%
Gurbuz G et al. [25]	GERD 33.3% Vomiting 33.3%	Dyslipidemia 16.7%	—	Weight loss 33.3%
Ismayilova N et al. [26]	Constipation Vomiting	Dyslipidemia 38%	—	—

KD: Ketogenic Diet, GI: Gastro-intestinal, GERD: Gastro Intestinal Reflux Disease

Discussion

The utilisation of the ketogenic diet is increasingly prevalent on a global scale as a viable therapeutic approach for the management of refractory childhood epilepsy. The research incorporated in this analysis was done in a diverse range of seven nations spanning across the globe. The findings of this review partially demonstrate the impact of the diet on a worldwide scale. Furthermore, the participants included in the review spanned from birth to 12 years of age, and the duration of the follow-up period ranged from 1 month to 24 months. Hence, this review provides a comprehensive summary of the existing knowledge regarding the immediate and prolonged effects of Ketogenic diet on children across various age cohorts. However, it is imperative to take into account ethnic disparities when utilising the findings of this review as a point of reference.

Types of ketogenic diet

The present review revealed that the majority of the participants started on the classic ketogenic diet with a ratio of 3:1 (55.6%), while around one-third (34.2%) were on the classic 4:1 ketogenic diet. The modified Atkin Diet was introduced in 23.9% of the participants. The classic ketogenic diet ratio of 3:1 is the most commonly utilised and highly recommended kind of KDT throughout infancy due to its ability to adequately fulfil protein needs and support optimal growth The ratio may be modified in accordance with factors such as acceptability, side effects, ketosis, or intercurrent circumstances [28,29].

Efficacy of the ketogenic diet

The utilisation of Ketogenic diet was initially documented by Douglas R et al. [30] in a study involving 32 newborns, and their findings demonstrated comparable outcomes. A total of 20% of the patients in their study achieved seizure freedom, while an additional 35% exhibited a favourable response. Several recent studies have provided further confirmation of the positive outcomes associated with ketogenic dietary therapy in the management of infantile spasms, which is the predominant form of seizure observed in infants [31,32].

Multiple studies have substantiated the effectiveness of the ketogenic diet and have demonstrated a reduction in seizure frequency of at least 50% for both the conventional Ketogenic diet and the modified Atkins diet [33]. The results of our study indicate that after one month, 54% of the participants reported seizure resolution, after three months of ketogenic diet 58% of the participants had seizure resolution. Similarly, after six, twelve and twenty-four months, 46.8%, 56.1% and 41.5% of the participants developed seizure resolution, respectively. While, after one, three, six, twelve and twenty-four months, 17%, 25.7%, 33.3%, 21.3% and 18.8% of the participants became seizure-free, respectively in this review, which was higher than those observed by Rezaei S et al. [34] and Sondhi V et al. [35]. Furthermore, the efficacy of the ketogenic diet (KD) treatment demonstrated a major improvement over three to six months.

Studies have demonstrated the efficacy of the ketogenic diet in treating epileptic syndromes, including myoclonic-astatic epilepsy, Rett syndrome, West syndrome (especially when associated with tuberous sclerosis), as well as Dravet and Doose syndromes [36,37,38]. In the present review, El-Shafie AM et al. [20] observed that all patients with focal seizures, and more than half of patients with generalised tonic-clonic seizures, infantile spasms, myoclonic seizures achieved seizure resolution after the initiation of the ketogenic diet. Based on a recent review, it has been determined that ketogenic diet exhibit both safety and efficacy in the treatment of drug-resistant epilepsy, GLUT1DS, and pyruvate dehydrogenase deficiency in children who are two years of age or younger [39].

Retention rate and long-term management

The researchers from the Ketogenic diet study have reached the conclusion that it is advisable to maintain the Ketogenic diet therapy for a minimum duration of three months in order to properly assess its effectiveness [40]. In relation to the objective and strategic approach for long-term management, there has been a notable reduction in the retention rate within

the present review. The three-months retention rate was 80.4%, while with subsequent follow-up the retention rate reduced further, such as 53.0%, 53.8% and 28% at the end of 6, 12 and 24 months, respectively. These findings demonstrate similarity to the outcomes reported in previous research investigations [41,42]. Efforts aimed at enhancing patients' adherence to ketogenic dietary therapy have the potential to concurrently enhance its efficacy [43]. It is crucial for caregivers to be willing to apply ketogenic diet therapy [44]. The proliferation of internet technology has significantly enhanced the accessibility of various aspects of long-term management, including effective contact with multidisciplinary teams and the provision of video-based instruction for novel ketogenic diet recipes [45]. Furthermore, there has been an improvement in the adaptability of the ketogenic diet in terms of its variations, and there has been a relaxation of limitations pertaining to calorie and fluid consumption in recent times [46].

Safety of ketogenic diet

The ketogenic diet is considered to be a reasonably safe and well-tolerated dietary intervention for children who suffer from refractory epilepsy. The occurrence of Ketogenic diet side effects is often attributed as a significant factor leading to trial dropouts, as they are commonly noticed in a substantial proportion of the young patient population [47]. A comprehensive analysis revealed the presence of over forty distinct adverse events, with notable prevalence observed in the cardiovascular, renal/genitourinary, skeletal systems, and gastrointestinal tract (mostly manifesting as constipation). While the studies included in the analysis did disclose a series of adverse events, it is worth noting that severe adverse events were few. In order to ensure the safe implementation of ketogenic diet therapy, it is recommended that children undergoing this dietary intervention have regular follow-up and monitoring for any adverse events.

A comprehensive analysis revealed the presence of adverse events, with the cardiovascular, renal/genitourinary, skeletal systems and gastrointestinal systems (mostly constipation) exhibiting the highest incidence rates [48,49]. The present review findings indicate that gastrointestinal adverse events were the most often observed. Specifically, constipation was reported in 30% of patients.

Another frequently reported side effect in the present review was dyslipidaemia (20%), Coppola et al. [50] and Kossoff et al. [51] confirmed this finding in a series of investigations conducted between 2006 and 2008, where they noted a concurrent rise in both total cholesterol and LDL levels. The lipid profile exhibits variations, particularly within the initial 12 months of implementing the diet, as reported in a significant proportion of children [48]. These variations may manifest within the first month of initiating the diet, but typically resolve and return to normal levels within a few months after its introduction which may serve as a reliable measure for the safety of the cardiovascular system posed due to a high-fat diet [41,52]. Hypoglycaemia, hypocalcaemia and acidosis were also noted in the current review. It is worth noting that other studies have shown varying proportions of adverse events in their studies [48,53,54].

Effect of ketogenic diet on growth

In this review, we found conflicting results on growth, Israel et al. [23] reported weight gain while Gurbuz et al. [25] reported weight loss in their studies, respectively. The findings of systematic reviews have revealed divergent outcomes regarding the effects of the ketogenic diet (KD) on growth, with certain studies suggesting a positive advantage while others suggesting an adverse influence [52]. Inadequate caloric and protein consumption, the presence of acidosis or ketosis, the impact of underlying medical conditions and treatments, the individual's ability to ambulate, and associated endocrine alterations are among the causative factors contributing to impaired growth in children undergoing ketogenic dietary regimens [55,56]. The occurrence of growth retardation in children following a ketogenic dietary therapy has been documented in previous studies, which aligns with the findings observed in our own review. Furthermore, it has been suggested that younger children may face a higher susceptibility to this adverse effect, particularly when subjected to extended treatment [17,33,57].

Limitation

The presence of heterogeneity among the patients who were enrolled in the study included in this review had an impact on the observed lack of statistical significance. Another limitation observed in the studies was the occurrence of drop-out cases resulting from noncompliance.

The fundamental disadvantage of this review is the inclusion of the majority of retrospective studies, which may introduce certain biases. Additionally, relying on parental reports of seizure decrease increases the potential for subjective inaccuracies.

Conclusions

The ketogenic diet are efficacious and safe intervention for the treatment of epilepsy in children. The classic ketogenic diet ratio of 3:1 is widely recognised as the most recognised form of ketogenic diet. Although adverse effects are frequently observed, they are generally of a mild nature and can be easily managed. Vigilant surveillance plays a crucial role in identifying adverse reactions, dietary insufficiencies, and anthropometric irregularities. Based on the findings of this review, it can be concluded that the ketogenic diet, including both classic Ketogenic diet and the modified Atkins diet, is a viable and generally well-received therapeutic approach for managing refractory epilepsy in paediatric patients. Further investigation is warranted

to provide a more comprehensive understanding of the efficacy and appropriateness of utilising Ketogenic diet as a standalone treatment option, either as an initial course of therapy or following the discontinuation of all other drugs once optimal disease management has been achieved. The determination to choose this particular dietary regimen should additionally consider factors such as financial implications, personal preferences, and the safety of the treatment.

Declaration of Conflicting Interests:
The Authors declare that there is no conflict of interest.

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Effectiveness of a Ketogenic Diet in Children with Refractory Epilepsy: A Systemic Review

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