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Efficacy and safety of dietary therapies in drug-resistant pediatric epilepsy: A synopsis of the available evidence

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For over a century, ketogenic diets (KDs) have been known for their effectiveness in pharmacoresistant epilepsy. However, the popularity of dietary therapies has increased over the last two decades due to an improved understanding of the concept of pharmacoresistance. In this context, different dietary therapies ranging from classic KDs to less restrictive diets such as the modified Atkins diet (MAD) and low glycemic index therapy (LGIT) have been evaluated in studies. Several evidence synthesis reviews including systematic reviews, meta-analyses, and network meta-analyses have tried to answer the question of the comparative efficacy and safety of different dietary therapies (Table 1) [1–17]. However, the evidence for the comparative efficacy of different diets is not very robust.

Several Cochrane reviews and other systematic reviews and meta-analyses on KDs for epilepsy have been published from 2003 to 2024 (Table 1) [1–17]. Although the key results for KD versus usual care comparison have been similar across most reviews, these reviews show significant improvement in the quality and robustness of evidence on the subject (randomized studies have been published only over the last two decades; Table 1). The results for the comparison of different dietary therapies have not been conclusive with a trend toward less restrictive diets. This is likely due to likely small effect size which would need multiple large trials to measure. Furthermore, the quality of the published reviews has also improved over the years, with recent reviews being more systematic and focused on high-quality evidence [randomized controlled trials (RCTs)].

Efficacy: KDs vs. usual care

Martin-McGill et al (2018) reported an overview of KDs for pharmacoresistant epilepsy based on 15 publications (including 11 RCTs) [7]. Achievement of seizure freedom was reported in 55% of patients, while up to 85% had seizure reduction with the classical 4:1 KD group after 3 months. During treatment with MAD, nearly 25% of the patients were seizure-free and up to 60% of the children had achieved seizure reduction. Gastrointestinal (GI) adverse events (AEs) were the most commonly reported AEs requiring dietary therapy withdrawal [7]. In 2020, this was updated with two additional RCTs (a total of 13 RCTs) on KDs for pharmacoresistant epilepsy [6]. In comparison with usual care, children had achieved statistically significant seizure reduction and seizure freedom with KDs [6]. Ruan et al. (2022) reported an overview of 12 meta-analyses and 14 systematic reviews of dietary therapies for pharmacoresistant epilepsy [8]. This review noted that classical KDs were better at reducing seizure frequency than the MAD for patients with infantile epileptic spasms syndrome (IESS), while ketogenic therapies were a success in seizure reduction in children and adolescents with other pharmacoresistant epilepsies. Additionally, approximately similar short-term and long-term efficacy outcomes were observed in different types of epilepsy [8]. In infants with pharmacoresistant epilepsy, a recent trial comparing classic KDs with antiseizure medications did not find any significant difference between diet and medications in terms of efficacy and tolerability [18, 19].

Efficacy: Comparison of different KDs

Most of the original research studies had compared the dietary therapies with care as usual. Only one RCT comparing KDs, MAD, and LGIT in childhood pharmacoresistant epilepsy reported that LGIT and MAD did not meet the non-inferiority criteria [20]. A recent network meta-analysis collating both direct and indirect evidence on the comparative efficacy and safety of different dietary interventions by our group suggests

Table 1. Summary of published systematic reviews and meta-analyses on KDs in drug refractory epilepsy

S. no	Author, year	Type of study	Number of patients and studies included	Intervention vs. comparator	Efficacy results	Safety results	Conclusion
1.	Devi N, et al., 2023 [2]	Systematic review and network meta-analysis	12 RCTs with 907 children	KD, MAD, and LGIT	All dietary interventions had shown greater efficacy than care as usual for 50% or higher seizure reduction (LGIT: OR = 24.7; 95% CI = 5.3−115.4; MAD: OR = 11.3; 95% CI = 5.1−25.1; and KD: OR = 8.6; 95% CI = 3.7−20.0)	AE-related discontinuation rates were highly significant with KD (OR = 8.6; 95% CI = 1.8−40.6) and MAD (OR = 6.5; 95% CI 1.4−31.2) compared with care as usual	All dietary therapies were effective for short term. However, MAD had better tolerability, higher probability for 50% or higher seizure reduction, and comparable probability for 90% or higher seizure reduction, and may be a sounder option than KD
2.	Diez-Arroyo C, et al., 2023 [10]	Systematic review of reviews	21 systematic reviews (8 systematic including 2 meta-analysis and 13 unsystematic) in children and adolescents	Classic KD, MAD, MCT-KD, and LGIT	Systematic reviews reported reduction in seizure frequency of ≥50% in about half of the patients. Reviews without systematic methodology showed ≥50% reduction in seizures in 30%–60% of children	The most frequent AEs in systematic reviews were: vomiting (6/8), constipation (6/8), and diarrhea (6/8); and in unsystematic reviews: vomiting and nausea (10/13), constipation (10/13), and acidosis (9/13).	KD can be effective in DRE ≥50% seizure reduction in half of the patients
3.	Mutarelli A, et al., 2023 [14]	Systematic review and meta-analysis of RCTs	6 RCTs with 575 patients (both adults and children; 288 MAD)	MAD vs. usual diet	MAD showed a higher rate of ≥50% seizure reduction (RR = 6.28; 95% CI = 3.52–10.50), both in children (RR = 6.28; 95% CI = 3.43–11.49) and adults with DRE (RR = 6.14; 95% CI = 1.15–32.66) MAD also had higher seizure freedom rate (RR = 5.94; 95% CI = 1.93–18.31)	AEs include constipation (17%; 95% CI = 5–44), lethargy (11%; 95% CI = 4–25), and anorexia (12%; 95% CI = 8–19).	MAD led to higher rates of seizure freedom and ≥50% seizure frequency reduction in both adults and children, with no significant AE concerns.
4.	Manral M et al., 2023 [12]	Systematic review and meta-analysis of RCTs	3 RCTs with 142 adolescents and adults	MAD vs. usual diet	Pooled proportion with ≥50% seizure reduction with MAD was 0.23 (95% CI = 0.10−0.37). The RR as compared with control group was 6.47 (95% CI = 1.60−26.14)	-	MAD therapy was efficacious and had better compliance for seizure reduction in subjects with DRE
5.	Ruan Yue et al., 2022 [8]	Overview of systematic reviews and meta-analyses	24 systematic reviews and meta-analyses encompassing a total of 255 original studies	Any KD intervention	Positive effects of KDs for epilepsy on seizure frequency reduction, as well as cognition and behavior, were observed. In contrast, the effects of KDT on quality of life, growth, and development were more controversial	The most prevalent AEs were GI, weight loss, and metabolic disorders, while the most common reasons for discontinuance were the lack of observed efficacy and dietary intolerance	KDs are safe and efficacious interventions for seizure reduction in DRE
6.	Mhanna A et al., 2022 [13]	Systematic review and meta-analysis of observational and interventional studies	6 studies, with 397 children with DRE (201 followed MAD vs. 196 with KD)	MAD vs. traditional KD	A significant difference in the proportion of patients who attained SFR >50%, favoring the traditional KD (RR = 0.63; 95%CI = 0.47−0.83)	Both regimens had comparable safety profiles (RR = 1.00; 95%CI = 0.95−1.05).	Traditional KD was superior to MAD for SFR ≥50% at 6 months in children with DRE. However, SFR >90% and seizure freedom were comparable between KD and MAD

(*Continued*)

Table 1. Continued

S. no	Author, year	Type of study	Number of patients and studies included	Intervention vs. comparator	Efficacy results	Safety results	Conclusion
7.	Desli E et al., 2022 [9]	Systematic review of RCTs	1114 children in 14 RCTs	Any KD vs. control group	A statistically significant seizure reduction by ≥50% in KD-treated group compared with control group in 6 of 14 studies over 3–4 months of follow-up	GI symptoms were the most frequent AEs	KD is an effective treatment for DRE in children and adolescents
8.	Lyons L et al., 2020 [11]	Systematic review and meta-analysis of RCTs	534 infants in 33 studies (2 RCTs and rest uncontrolled cohort studies)	Any KD	Meta-analyses of uncontrolled studies revealed that 59% (95% CI = 53−65) of infants achieved ≥50% seizure reduction and 33% (95% CI = 26−43) of infants achieved seizure freedom	Retention rates ranged from 84% at 3 months to 27% at 24 months. AEs included dyslipidemia (12%), vomiting (6%), constipation (4%), gastroesophageal reflux (4%), and diarrhea (4%)	KDT is a safe, tolerable, and effective treatment option for infants with DRE
9.	Martin-McGill KJ et al., 2020 [6]	Systematic review of RCTs or quasi-RCTs	13 studies with 932 participants; 711 children (4 months to 18 years) and 221 adults (16 years and above)	KD vs. usual care and KD vs. KD for children and adults	Children: Seizure freedom (RR = 3.16, 95% CI = 1.20−8.35) and seizure reduction (RR = 5.80, 95% CI = 3.48−9.65) favored KDs over usual care. Classic KD: SFR = 55%, SRR = 85%; MAD: SFR = 25%, SRR = 56% Adults: Seizure reduction favored KDs (MAD only) over usual care (RR = 5.03, 95% CI = 0.26−97.68; P = 0.29)	The most commonly reported AEs were vomiting, constipation, and diarrhea	KDs could demonstrate effectiveness in children with DRE. However, the evidence for KDs in adults remains uncertain
10.	Sourbron J et al., 2020 [16]	Review and meta-analysis	5 RCTs (7 publications) with 472 children and adolescents	Any KD vs. control	Significant efficacy of the KD compared with the control group: RR = 5.1 (95% CI = 3.18–8.21, p < 0.001).	GI AEs were the most prevalent, and no severe AEs were reported.	Despite heterogeneity, evidence supports KDs for children with DRE not amenable to surgery
11.	Wang YQ et al., 2020 [17]	Meta-analysis	7 studies with 167 patients with Dravet syndrome	Any KD vs. control	63%, 60%, and 47% of responder patients achieved ≥50% seizure reduction at months 3, 6, and 12, respectively	The pooled retention rate of KDs at month 6 and month 12 was 78% and 49%, respectively	KD is a safe treatment option for patients with Dravet syndrome
12.	Martin-McGill KJ et al., 2018 [7]	Systematic review of RCTs or quasi-RCTs	11 RCTs with 778 patients (712 children and adolescents and 66 adults)	Any KD vs. control group	SFRs of up to 55% and 25% with classic KD and MAD, respectively. SRRs of 85% and 60% with classic KD and MAD, respectively.	The most commonly reported AEs were GI syndromes, more with classic KD	Promising results for the use of KDs in epilepsy
13.	Rezaei S et al., 2017 [15]	Systematic review and meta-analysis of observational and interventional studies	70 studies with children and adolescents	Classic KD and MAD	A non-significant trend toward a higher efficacy of MAD at month 3 and month 6 (P > 0.05). In the classical KD group, the proportion achieving ≥50% seizure reduction was 62, 60, 52, 42, and 46% at months 1, 3, 6, 12, and 24 and for the MAD group was 55, 47, 42, and 29% at months 1, 3, 6, and 12, respectively	-	Classical KD does not differ substantially from MAD in ≥50% and ≥90% SRRs at month 3 and month 6, respectively

(*Continued*)

Table 1. Continued

S. no	Author, year	Type of study	Number of patients and studies included	Intervention vs. comparator	Efficacy results	Safety results	Conclusion
14.	Cai QY et al., 2017 [1]	Systematic review and meta-analysis of prospective studies	45 studies including 7 RCTs	Classic or MCT-KD	-	The total retention rates for 1 year and 2 years were 45.7% and 29.2%, respectively. Nearly half discontinued KD due to inefficacy. Most common AEs included GI disturbances (40.6%), hyperlipidemia (12.8%), hyperuricemia (4.4%), lethargy (4.1%), infectious diseases (3.8%), and hypoproteinemia (3.8%). Severe AEs were rare	KD is a relatively safe dietary therapy
15.	Martin K et al., 2016 [5]	Systematic review of RCTs or quasi-RCTs	7 RCTs with 427 children and adolescents	Any KD vs. control group	SFRs of up to 55% and 10% with classic KD and MAD, respectively. SRRs of 85% and 60% with classic KD and MAD, respectively	The most commonly reported AEs were GI syndromes	Promising results for the use of KDs in epilepsy
16.	Levy RG et al., 2012 [4]	Systematic review of RCTs	289 children in 4 RCTs	Any KD vs. control group	Short- to medium-term benefits in seizure control. Meta-analysis not done due to heterogeneity	The main reasons for drop-outs in the included studies included GI side effects and dislike for the diet.	KD results in short- to medium-term benefits in seizure control
17.	Levy RG and Cooper PP, 2003 [3]	Systematic review of RCTs	No RCTs found	KDs vs. control	No evidence from RCTs to support KDs, but observational studies do lend some support for a beneficial effect	-	No evidence from RCTs to support KDs, but beneficial effect seen in observational studies

RCTs: randomized controlled trials; KD: ketogenic diet; MAD: modified Atkins diet; LGIT: low glycemic index therapy; OR: odds ratio; CI: confidence interval; AEs: adverse events; MCTs: medium-chain triglycerides; DRE: drug-resistant epilepsy; RR: risk ratio; KDT: ketogenic dietary therapy; GI: gastrointestinal; SFR: seizure freedom rate; SRR: seizure reduction rate.

that MAD is a better option as compared with classic KDs considering their better safety profile and similar efficacy. However, there is a scarcity of evidence for LGIT (otherwise the safest option) [2]. Hence, a large head-to-head trial comparison of different dietary therapies is very much needed.

Safety

Despite their good efficacy, the withdrawal rate for KDs has been higher due to intolerable AEs. Although the most common reason for discontinuation is the lack of efficacy, common AEs include GI issues [1]. Besides, palatability also plays a role as the withdrawal rate was less frequent in children younger than 2 years because parents/caregivers can easily control their diet and food behavior in young age than that in older children or adults [11].

Low- and middle-income country perspective

Cultural differences, taste, and religious preferences influence the ability to adhere to strict dietary therapies, especially in older children, adolescents, and adults. In many low- and middle-income countries (LMICs) like India, the observance of vegan and vegetarian diets is often based on cultural and family beliefs inculcated since early childhood. However, these limit the edible options in the KDs, affecting dietary compliance. Furthermore, the presence of neurological comorbidities such as intellectual disability and neurodevelopmental disorders like autism spectrum disorder also impact the adherence to diet.

Indigenous foods are an integral part of traditional food systems. They can enhance the adherence to diets without significantly affecting the patient's and family's beliefs, thereby increasing acceptability. Many large research studies and clinical trials on KDs in controlled settings have been done in the LMICs and have demonstrated similar efficacy for KDs in pediatric epilepsy in LMICs [20–22]. Furthermore, the efficacy might be affected by the age group (infancy) and specific epilepsy syndromes as evident in the recent KIWE trial which failed to demonstrate a significant difference between diet and medications in terms of efficacy and tolerability [18]. The implications of this trial for LMICs are likely significant considering the preponderance of structural etiology and huge diagnostic lags for IESS, which might further impact the efficacy in real-world settings [19, 23].

The cost of indigenous foods is likely to be low as compared to antiseizure medications (ASMs). Hence, indigenously designed and prepared diets may be a good option for LMICs. However, the current evidence profile of KDs has shown an inconclusive cost-effectiveness profile in high-income countries [24, 25]. Future studies are needed to evaluate the cost-effectiveness of dietary therapies in LMICs.

Limitations of dietary interventions

Nevertheless, the available evidence on KDs has limitations. The quality of the included studies in most of the available reviews was rated as low to very low. Limitations of sample size and comparison groups were the most probable reason for the uncertain quality of evidence. Furthermore, a great deal of clinical heterogeneity has been identified in the included studies, including seizure types (epileptic spasms, drop seizures, and absences), epilepsy syndromes, patient age, etiologies, and concurrent antiseizure medication use. Also, the research studies have evaluated subjective symptomatic outcomes by using seizure records maintained by the parent or caregiver, and clinical identification of seizure types may be difficult in epileptic encephalopathies. Consequently, the lack of standardized clinical measurement tools still haunts epilepsy research, especially in low-resource settings [video electroencephalogram (EEG) adds to the cost]. Long-term EEG is the best outcome measure for the detection of seizures and their frequency. Ideally, it should also be added as an outcome measure to detect electrographic seizures during the treatment with dietary therapies. The measures of the evaluation of dietary compliance (ketone bodies for KDs) have not been established for MAD and LGIT.

To conclude, although many research studies have been done and published on dietary therapies in pediatric pharmacoresistant epilepsies, a summary of evidence should be looked at considering the limitations in the field of epilepsy research. With accumulating evidence, a synopsis of evidence becomes very important to understand the utility and comparative efficacy and safety of dietary therapies. Furthermore, large head-to-head trials comparing different dietary therapies are the need of the hour. Also, future studies are needed to evaluate the cost-effectiveness of dietary therapies in LMICs.

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Competing interests

None.

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Nagita Devi and Priyanka Madaan were involved in the literature review and prepared the initial draft of the manuscript. Priyanka Madaan, Jitendra Kumar Sahu, and Dipika Bansal were involved in the literature review and critical review of the manuscript for intellectual content. All authors contributed to and approved the manuscript for submission.

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