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Original Article

Is the Ketogenic Diet Effective and Safe in Children with Intractable Epilepsy? A Systematic Review

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Abstract:

Background: The ketogenic diet (KD) has long been prescribed to children with recurrent epilepsy due to its minimal neurotoxic effects. The side effects caused this diet to be abandoned. New diets are emerging as options such as modified Atkins diet (MAD), low glycemic index therapy (LGIT) and medium-chain triglyceride (MCT). This study compared the safety and effectiveness of the KD and these new methods.

***Method*:** Systematic review was conducted by searching databases such as PubMed, ScienceDirect, SpringerOpen, Cochrane, Proquest and Scopus based on the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) guidelines.

Result: : A total of 439 pediatric patients aged 0 - 18 years who were intervened with a ketogenic diet compared with other dietary options. A total of five studies reported a higher mean reduction in seizure incidence >90% in children who were intervened with a ketogenic diet compared to other diets, one of which reported KD > MAD (53.3% KD vs. 26.6% MAD).

***Conclusion*:** Although KD remains effective, MAD, LGIT, MCT and Polyunsaturated Fatty Acids KD (PUFAKD) diets provide comparable benefits with potential for better adherence. The classic KD group showed a higher morbidity rate; however, it demonstrated significant effectiveness in lowering the incidence of recurrent seizures in children.

Keywords: children, intractable epilepsy, ketogenic diet

Introduction

Epilepsy is a chronic neurological condition that affects over 50 million people of all ages and sexes worldwide. The prevalence of epilepsy is disproportionately concentrated in low and middle-income countries (LMICs).[1] Epilepsy contributes to a significant disease burden in children and adolescents worldwide. Globally, more than 11 million children aged less than 15 years have active epilepsy.[2] In 2017, more than 291 million children aged less than 20 had epilepsy and intellectual disabilities, of which 95% lived in low- and middle-income countries.[3]

The main goals of epilepsy treatment include three basic issues: achieving the best possible seizure control, avoiding the undesired effects of treatment, and maintaining/improving the quality of patients' lives. Therefore, numerous attempts are made to offer alternative treatments for drug-resistant seizures, an example of which is the ketogenic diet.[1]

The classic ketogenic diet (KD) is a high-fat, low-carbohydrate diet, in which fat, instead of glucose, acts as a major energy source through the production of ketone bodies. The KD was formally introduced in 1921 to mimic the biochemical changes associated with fasting and gained recognition as a potent treatment for pediatric epilepsy in the mid-1990s.[4]

Although its efficacy is proven, KD is not an easy and convenient method of treatment to both patients and caregivers. Maintaining a high-fat diet can be unpalatable and result in various adverse effects. Preparing each meal with calculation and measurement of food composition and ingredients can be impossible to some patients and caregivers. Therefore, alternatives to the classic KD have been developed and studied.

Currently, four main KDs are used in clinical practice: KD, the medium-chain triglyceride (MCT) diet, the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT). The efficacy of the three KD alternatives MCT, MAD, and LGIT has been compared to that of classic KD in various studies, including randomized controlled trials. When KDs must be maintained for several years because of seizure recurrence or clinical course of the disease, it is reasonable to consider switching to alternatives to the classic that have been developed and studied. MAD or LGIT were developed as less restrictive and more palatable options to the classic KD when considering the risks of long-term complications.[1]

In this systematic review we want to find out a comparison efficacy and safety of the alternative models of MCT diet, MAD, and LGIT compared to the classic KD in reducing seizures.

Method

Literature Search

We explored PubMed, ScienceDirect, ProQuest Dialog (PQD), Cochrane and Springer Open from articles published in the recent 10 years November, 2009 to November, 2024 using the following keywords (MesH Term) of "child", "pediatric", "ketogenic diet", "keto diet", "intractable epilepsy", "refractory epilepsy", "safety", "adverse effects", "efficacy", "effectiveness", "seizure reduction", "morbidity outcome".

Online scientific articles were first screened by title and abstract based on the following inclusion criteria: publication in English, cohort and randomized-controlled trial study design focusing on Ketogenic Diet (KD) versus other dietary option with outcomes of seizure reduction incidence and adverse effects of diet; the study subject age <18 years and diagnosed with intractable epilepsy. The exclusion criteria were unavailable online full-text publication; systematic-reviews; meta-analyses; informal literature review. The results were presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline (**Figure 1**).

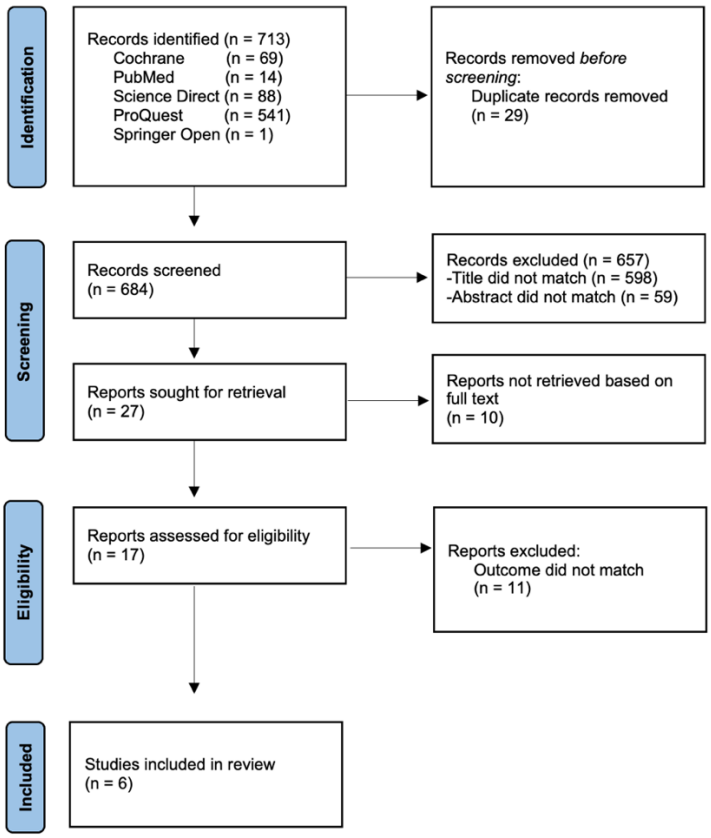

Figure 1. PRISMA flowchart on study screening and selection process.

Ketogenic Diet

The classic KD has been used worldwide as a well-established treatment for intractable epilepsy with expanding indications, especially in the neuro-metabolic field. KD is a high-fat, low-carbohydrate, and adequate-protein diet designed to induce ketosis; a state that has been shown to reduce seizure frequency in many patients. It consists of the ratio of 70-80% fat, 10-20% protein, and less than 10% carbohydrate.[5] The KD has several types, including the classical KD, MCT, Polyunsaturated Fatty Acids KD (PUFAKD), MAD, and LGIT.[6-8]

The classical KD is the original form of the ketogenic diet, developed in the 1920s primarily to treat drug-resistant epilepsy, particularly in children. KD uses a 4:1 ratio of fat to combined with LCT and carbohydrates. The MCT is a variation of the ketogenic diet that incorporates medium-chain triglycerides (MCTs) as the primary fat source. MCTs promotes faster ketosis due to quicker liver absorption. PUFAKD is another variation of ketogenic diet which emphasizes the inclusion of polyunsaturated fatty acids (PUFAs) as the primary fat source. PUFAs incorporates omega-3-rich fats for anti-inflammatory benefits in seizure control. Moreover, MAD is less restrictive variation of ketogenic diet, allowing more protein and easier adherence. MAD focuses on limiting carbohydrates to induce ketosis while allowing for greater flexibility in protein and fat intake. It was developed as an alternative for individuals, particularly those with epilepsy, who find the classical ketogenic diet too rigid or challenging to follow.[6-8]

Another dietary approach used to manage epilepsy is LGIT. While both KD and LGIT aim to reduce seizures by altering the brain's energy metabolism, LGIT focuses on limiting high-glycemic foods to stabilize glucose, minimizing spikes in insulin.[6-8]

Data Extraction

Titles and abstracts retrieved from the database were independently screened by five reviewers to identify relevant studies that met the selection criteria outlined above, who also independently assessed eligibility by further reviewing the full text. Disagreements were resolved through consultation with a sixth reviewer. Data from the articles then were extracted, including lead author, year of publication, type of study, country, age of subject, age of seizure onset, number of subjects, type of intervention, follow-up period, frequency of daily seizure, record method of seizure, incidence of seizure reduction, and adverse effect of diet. The reviewers extracted data independently and discrepancies were identified and resolved in consultation with other reviewers. The selection process is shown in the PRISMA 2020 flow diagram (**Figure 1**).

Result

There were 713 articles found based on the literature search, of which 6 identified as relevant to the topic and met the inclusion criteria. The articles included were Randomized controlled trials published from November 2009 - November 2024. A total of 564 pediatric patients aged 0 - 18 years who were intervened with a ketogenic diet compared with other dietary options such as PUFAKD, MAD, LGIT and KD 2,5:1 was studied. The subject characteristics are shown in **Table 1.**

Cases of seizure free children were reported in two study where the classic ketogenic diet reported a higher number of seizure free cases compared to the modified atkins diet (53.3% vs 26.6% and 60% vs 46.67%) as shown in **Table 2** and **Table 3**, while other study reported a higher number of seizure free cases in polyunsaturated fatty acids ketogenic diet compared to the classic ketogenic diet (37% vs 32%) as shown in **Table 3**. During the 2 follow up periods month 3 and 6 (**Table 2** and **Table 3**), a total of three studies reported a higher mean reduction in seizure incidence >90% in children who were intervened with a ketogenic diet compared to other diets, three of which reported KD > MAD (37% KD vs. 32% MAD; 6.6% KD vs. 0% MAD; 37% KD vs. 30% MAD)[16,17,18,21,22]. Four studies also reported a higher mean reduction in seizure incidence 50-90% in children who were intervened with a ketogenic diet, four of which reported KD > MAD (43% KD vs. 42% MAD; 45.8% KD vs. 45.5% MAD; 44.2% KD vs. 25.0% MAD; 39% KD vs. 36% MAD)[17,18,21,22].

A higher percentage of gastrointestinal adverse events such as vomiting, diarrhea, and constipation was reported in all studies of KD compared to MAD. Incidence of kidney stones was reported higher in KD compared to MAD group (4 % vs. 0%; 8.3% vs. 0%)[17,21]. During the 6-month follow-up period, ketogenic hypercholesterolaemia was also shown to be higher in the KD group than the MAD group (14 % vs. 11 %; 8.3% vs. 0%) as shown in **Table 4**[17,21].

Discussion

Classic KD is a low-carbohydrate and high-fat diet, that is considered wildly successful in treating children with recurrent epilepsy and seizure.[9-11] Throughout the history of neurological medication, KD was deemed efficient due to its minimal neurotoxic effects. The main features of a KD treatment are the production of ketone bodies, mainly β-hydroxybutyrate, acetoacetate, and acetone formed during the breakdown of fatty acids in the liver, along with a reduction in blood glucose levels. Ketone bodies serve as an alternative energy source to glucose and are also important for the development of the brain, providing essential materials for building cell membranes and lipids.[12] To improve dietary based treatment efficacy and flexibility, several variants of the KD have been developed as opposing factors to minimize side effects

that are commonly recorded in short-to-medium term benefits of neurological symptoms.[13]

The classic KD is effective for managing intractable epilepsy in children but can be difficult to maintain. This has led to alternative diets like the MAD, LGIT, and MCT diet, which aim to provide similar benefits with potentially easier adherence. MAD is a high-fat, low-carb diet with greater protein flexibility, without strict calorie counting. Studies show MAD can reduce seizure frequency similarly to KD and may be easier to follow for some families.[14] LGIT emphasizes low-glycemic carbs to stabilize blood sugar. Research suggests LGIT can significantly reduce seizures and may be easier to adhere to than KD.1 Medium-chain triglyceride diet uses to induce ketosis with a higher carbohydrate allowance, potentially making it more palatable. Studies show it to be as effective as KD in seizure reduction, with fewer side effects for some patients.[15]

In this study, we conducted a systematic review of studies focusing on effectiveness and safety of classic KD compared to MAD, LGIT, MCT and KD 3:1 and KD 2.5:1. We focused on seizure recurrence and diet-related side effects, assessing outcome reductions after 3 and 6 months.

In the 3 months follow up, the efficacy percentage of the control group (KD) showed higher results in >90% outcome reduction in recurrent seizures compared to other methods (6.67% vs 0%; 21% vs 27%; 32% vs 37%; 26.6% vs 53.33%), respectively written "case" vs "control".[16-18] This result was also in line with a RCT study that stated efficacy of KD during the 4 months follow up was evidently effective in reducing recurrent seizure.[19] Although this outcome was regarded as comparable in efficacy by a study conducted in 2021, other studies have shown that using modified KD 2.5:1 granted more efficacy in seizure control due to fewer adverse events, with no significant difference in the biochemical parameters as compared to other modified KD ratio.[16,20]

To further verify the efficacy and safety of KD, results from other methods have showed that >50%-≤90% seizure reduction were more significant compared to KD in 3 months follow up, with reports of MCT and modified KD in the intervention group presented higher results (63% vs 58%).[16] However, one study conducted by Kim et al. presented a different result, where the control group using KD was proven more effective in >50%-≤90% reduction of recurrent seizure as compared to modified KD (42% vs 43%).[17]

Table 1. The Characteristics of Subjects

No	Author (year)	Type of Study	Study Location	Mean age, month (SD)		Type of Intervention				Follow-up Period (month)	Mean age at onset of seizure, month (SD)		Mean daily seizure frequency, n (SD)	
				Case	Control	Case	Sample (n)	Control	Sample (n)		Case	Control	Case	Control
1	Raju et al, 2011[16]	RCT	India	2.8 (1.1)		KD 2,5:1	19	KD	19	3	NR		47.8 (38.5)	
2	El-Shafie et al, 2023[18]	RCT	Egypt	48-85a		MAD	15	KD	15	3, 6	21.5-55a		10	
3	Poorshiri et al, 2021[21]	RCT	Iran	4.5 (1.5)		MAD	15	KD	30	6	NR		NR	
4	Sondhi et al, 2020[23]	RCT	India	5.2 (3.2)		MAD	58	KD	55	6	0.7 (1.4)		20.1 (31)	
						LGIT	57							
5	Kim et al, 2016[17]	RCT	Korea	4.9 (4)		MAD	53	KD	51	3, 6	2.3 (2.8)		4.6 (NR)	
6	Ray et al, 2024[22]	RCT	India	55.2 (27.6)	49.2 (15.6)	PUFA KD	27	KD	25	6	57 (27.47)	50 (26.03)	75.62 (17.7)	62.6 (16.4)

RCT = Randomized Controlled Trial, a = Interquartile range is reported, KD = Classic Ketogenic Diet, MAD = Modified Atkins Diet, LGIT = Low Glycemic Index Therapy, PUFAKD = Polyunsaturated Fatty Acids Ketogenic Diet, NR = Not Reported

Table 2. Outcome of Seizure Reduction in 3 Months

Author , year	Type of Intervention, Sample Size		Seizure free, n (%)		>90% Seizure Reduction, n (%)		90-50% Seizure Reduction, n (%)		<50% Seizure Reduction, n (%)	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
El-Shafie et al, 2023[18]	MAD, 15	KD, 15	4 (26.6)	8 (53.3)	1 (6.67)	0 (0)	8 (53.3)	6 (39.9)	2 (13.3)	1 (6.67)
Kim et al, 2016[17]	MAD, 53	KD, 51	NR	NR	17 (32)	19 (37)	22 (42)	22 (43)	NR	NR
Raju *et al*, 2011[16]	KD 2,5:1, 19	KD, 19	NR	NR	4 (21)	5 (27)	12 (63)	11 (58)	NR	NR

MAD = Modified Atkins Diet, KD = Classic Ketogenic Diet, LGIT = Low Glycemic Index Therapy, PUFAKD = Polyunsaturated Fatty Acids Ketogenic Diet, NR = Not Reported

Table 3. Outcome of Seizure Reduction in 6 Months

Author , year	Type of Intervention, Sample Size		Seizure free, n (%)		>90% Seizure Reduction, n (%)		90-50% Seizure Reduction, n (%)		<50% Seizure Reduction, n (%)	
	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
El-Shafie et al, 2023[18]	MAD, 15	KD, 15	7 (56.67)	9 (60)	0 (0)	0 (0))	7 (46.67)	5 (53.33)	1 (6.67)	1 (6.67)
Poorshiri et al, 2021[21]	MAD, 15	KD, 30	NR	NR	0 (0)	2 (6.6)	5 (45.5)	11 (45.8)	NR	NR
Sondhi et al, 2020[23]	MAD, 58	KD, 55	NR	NR	6 (11.5)	6 (11.5)	13 (25)	23 (44.2)	14 (26.9)	13 (25)
	LGIT, 57		NR	NR	8 (14.8)	-	15 (27.8)	-	15 (27.8)	-
Kim et al, 2016[17]	MAD, 53	KD, 51	NR	NR	16 (30)	19 (37)	19 (36)	20 (39)	NR	NR
Ray *et al*, 2024[22]	PUFAKD, 27	KD, 25	10 (37)	8 (32)	0 (0)	3 (12)	9 (33.3)	9 (36)	8 (29.6)	5 (20)

KD = Classic Ketogenic Diet, MAD = Modified Atkins Diet, NR = Not Reported

Table 4. Outcome of Adverse Effect

Author, year	Follow-up period, month	Type of Intervention, Sample Size (n)		Vomiting, n (%)		Diarrhoea, n (%)		Constipation, n (%)		Lack of Energy, n (%)		Severe Infection, n (%)		Renal Stone, n (%)		Hyper-cholesterolemia, n (%)	
		Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control	Case	Control
Kim et al, 2016[17]	3	MAD, 53	KD, 51	8 (15.0)	9 (18.0)	3 (6.0)	5 (10.0)	12 (23.0)	14 (27.0)	10 (19.0)	13 (25.0)	0 (0.0)	3 (6.0)	0 (0.0)	0 (0.0)	10 (19.0)	7 (14.0)
	6			2 (4.0)	2 (4.0)	0 (0.0)	1 (2.0)	10 (20.0)	9 (17.0)	1 (2.0)	2 (4.0)	2 (4.0)	0 (0.0)	0 (0.0)	2 (4.0)	6 (11.0)	7 (14.0)
Raju et al, 2011[16]	3	KD 2,5:1, 19	KD, 19	NR	NR	NR	NR	3 (15.7)	5 (26.3)	NR	NR	1 (5.2)	2 (10.5)	NR	NR	NR	NR
Poorshiri et al, 2021[21]	6	MAD, 15	KD, 30	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0 (0.0)	2 (8.3)	0 (0.0)	2 (8.3)
Ray et al, 2024[22]	6	KD, 25	PUFAKD, 27	4 (16)	13 (48.0)	1 (4.0)	5 (18.5)	7 (28.0)	7 (25.9)	1 (4.0)	-	NR	NR	NR	NR	NR	NR

MAD = Modified Atkins Diet, KD= Ketogenic Diet, PUFAKD= Polyunsaturated Fatty Acids Ketogenic Diet, NR= Not Reported

In a longer observation period of 6 months, classic KD was shown to achieve consistent results with a highly coherent in >90% or percentage in reducing the incidence of recurrent seizures >90% (30% vs. 37%; 46.7% vs. 60%; 0% vs. 6.6%; 0% vs 12%)[17-18,21- 22], compared to other diets. In contrast to the 3 months results, the classic KD group showed a higher percentage in reducing the incidence of recurrent seizures 50%-≤90% (36% vs. 39%;33.3% vs 36%;26.4% vs. 44.2%)[17,22-23], compared to the alternative diet. This proves that the classic KD has promising efficacy in the longer term. This outcome is in accordance with a study conducted in 2024, showing significant efficacy in 32% seizure free with classic KD in a 6 month study course.[22] To strengthen the previous scientific studies, a recent study in 2020 and 2024 showed the percentage reduction in recurrent seizure <50% higher in the alternative diet group.[22-23]

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In terms of diet safety at 3 months of observation, two studies reported no significant difference in classic KD compared to other diets for gastrointestinal disorders such as vomiting (15% vs. 18%)[17], diarrhea (6% vs. 10%)[17] and constipation (15.7% vs. 26.3%; 23% vs. 27%).[16-17] Studies conducted in 2019 and 2021 also stated, in a 3-month study follow up, results showed no significance in gastrointestinal adverse events, deeming classic KD to be safe have no basis for discontinuation.[28-29] Two studies reported adverse events of severe infection in classic KD and other dietary methods, both of which proved to be safe, characterized by an incidence rate of ≤10%.[16-17]

Gastrointestinal disorders were followed until 6 months of age, the incidence of vomiting showed inconsistent results with one study reporting a greater percentage in the control group than other diets, the rest showing similar percentages (4% vs. 4%; 16% vs. 48%), respectively.[17,22] Similarly, the incidence of diarrhea and constipation showed inconsistent results (0% vs. 2%, 4% vs. 18.5%) and (20% vs. 17%; 28% vs.

25.9%), respectively.[17,22] This finding is in line with a study in conducted in 2016 which stated similar outcomes regarding safety and efficacy of classic KD, that although classic KD remains significant in seizure reduction, along the study course of more than 3 months, emergence of gastrointestinal disorders would be apparent but insignificant.[30] Children who experienced a lack of energy showed that the alternative diet have a higher percentage (19% vs. 25%) than the classic KD in 3 month observation.[17] The incidence of serious infections dropped to 0% in the classic KD group after 6 months, this suggests that classic KD is not associated with these side effects.[11] This finding is consistent with that of a study in China, that adverse events of infections were deemed insignificant, and therefore regarded as unrelated to KD.31

One study conducted a long-term follow-up until 12 months of age, found that the percentage of gastrointestinal disorders in the form of vomiting and constipation was greater in the classic KD group (39% vs. 45%), respectively.[2] These results were in line with that of a recent study in 2023, in a 15-month study course, classic KD group showed a significant correlation with lower microbial diversity, therefore regarding KD's long term use as an underlying factor in emergence of gastrointestinal disorders such as vomiting, constipation, along with diarrhea.[32-33] This finding cohered with several studies in long term classic KD usage as key reasoning for gastrointestinal disorders. A recent systematic review in 2024 stated that gastrointestinal disorders were found more frequent in classic KD as compared to other methods although still deemed insignificant, therefore concluding that further observation is needed when diet in intractable epilepsy children is given.[34]

Nutritional therapy is not enough to treat intractable epilepsy. Recently, the American Academy of Pediatrics (AAP) strongly recommended the comprehensive therapy of both pharmacology and dietary intervention such as classic KD for intractable epilepsy, along with primary preventions of infections occurrences as well as trauma. Efficacy results in seizure reduction with KD were found in 3, 6 and 12 months, with reports of seizure free 3%, 3% and 11%, respectively.[35] Seizure reduction of 90-99% in 3, 6 and 12 months was also found significant by 31%, 29% and 20%, respectively[35], deeming KD as the dietary treatment of choice for the years heretofore. Routine observation of results and monitoring of adequate dietary treatment should be done accordingly in subsequent months to achieve optimal outcome and treatment compliance.

The principal strength of our study lies in its status as the first systematic review to evaluate the efficacy of classic ketogenic diets compared with alternative diets (MAD, LGIT, MCT, KD3:1, KD2.5:1, PUFAKD), focusing on seizure reduction and safety profile. We endeavored to conduct high-quality research in accordance with

established guidelines for such analyses, strictly adhering to the Cochrane Collaboration's recommendations on intervention studies.

Limitations include study heterogeneity, including a variety of countries where data were collected and a wide range of publication dates. There were also differences in the sample size of children, classic KD and other diets, duration of intervention, and dosage and compliance (information not available for all studies).

Conclusion

The classic KD remains highly effective in reducing recurrent seizures in children, despite its higher morbidity rate compared to alternative diets like MAD, LGIT, MCT, and PUFAKD. While these alternatives offer comparable benefits and may improve adherence, KD's proven efficacy makes it a valuable treatment option. Awareness of KD among pediatricians remains limited, partly due to its potential side effects, including gastrointestinal issues and adherence challenges. Professional guidance and further research are essential to optimize KD use and address its limitations.

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Conflict of Interest

None declared

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