Review Article
Journal of Epilepsy Research
pISSN 2233-6249 / eISSN 2233-6257

Modified Atkins Diet in Adolescents and Adults with Drug Resistant Epilepsy: A Systematic Review and Meta-Analysis

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Epilepsy is one of the common neurological diseases which affects 65-70 million people worldwide. Modified Atkins diet (MAD) as a therapy is used as one of the treatments to reduce the seizures occurrence in epileptic patients. The purpose of this purpose is to review all evidence regarding the efficacy of the MAD from randomized controlled trials (RCTs) in adolescents and adults with drug resistant epilepsy (DRE). The total of three databases were searched (PubMed, Embase, and Cochrane Library) till 31 January 2023. Only RCTs with MAD as a one of the treatment arms were included in meta-analysis. The proportion of reduction of seizures in patients with epilepsy and relative risk to identify the relationship between MAD (as risk) to decrease the epileptic seizure was used as outcomes. The Jadad score with three domains was used to estimate the quality of RCTs included for meta-analysis. Only three RCTs were included following the stringent inclusion criteria in current meta-analysis. The pooled proportion from 142 patients going through MAD therapy shows the reduction in epileptic seizure ≥50%, by the random effect model was 0.23 (95% confidence interval [CI], 0.10 to 0.37). Our meta-analysis underlines a significant efficacy of MAD compared to the control group in seizure reduction ≥50%, The pooled relative risk was 6.47 (95% CI, 1.60 to 26.14; *p*-value <0.05). MAD therapy was efficacious and had better compliance for seizure reduction in subjects with DRE. **(2024;14:1-8)**

Key words: MAD, Drug resistant epilepsy, Randomized control trials, Relative risk, Meta-analysis

Received November 21, 2023
Revised January 13, 2024
Accepted February 19, 2024

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Introduction

Epilepsy is one of the common neurological diseases which affects 65-70 million people worldwide.[1] Epilepsy is associated with a poorer health outcome, and a significant psychological and emotional burden leading to poor quality of life.[2] The major goals of the treatment are to achieve seizure freedom, improve the quality of life, and prevent side effects.[3] Drug-resistant epilepsy (DRE) is defined by the International League Against Epilepsy as failure of adequate trials of two tolerated appropriately chosen and used anti-seizure medications (ASMs) to achieve seizure freedom.[4] Approximately 70% of people with epilepsy (PWE) have a seizure that will be controlled with 1 or 2 ASMs.[5] Treatment options for DRE may include surgery, neuromodulation, and addition of dietary therapy.[6,7] About 20% to 30% of the PWE have DRE despite the growing number of all available ASM options.[5] In addition, ASMs cause significant adverse effects affecting the quality of life.[8] For many patients who are not suitable surgical candidates, other treatment modalities are possible such as vague nerve stimulation (VNS)[9] and dietary treatments like ketogenic diet (KD).[10] Seizure reduction is at least 50% in half of the patients on dietary therapy (KD or modified atkins diet [MAD]) which is higher as compared with VNS[11] and therefore added dietary options should be taken into consideration as it does not have neurotoxic effects in PWE.[12]

More recently there has been an increase in the number of trials investigating the efficacy in adults.[10,13] The first International recommendations for the management of adults treated with KD therapies were published in 2020.[14] The classical KD is a very low carbohydrate and high-fat diet which is difficult for adults and adolescents to comply with.[15]

In the last 20 years, new variants of KD have been introduced including the MAD, medium chain triglyceride, and low glycemic index diet.[12] These diets are less restrictive and well tolerated in the context of a multifaceted approach to help attain better seizure control.

The exact mechanism of seizure reduction with diet therapy is still under investigation and ketone bodies could exert anti-oxidative, anti-inflammatory, cellular, epigenetic, and gut-microbiome alterations.[15-17] The efficacy of KD in childhood epilepsy is well tolerated.[18-21] However, studies on the efficacy and tolerability of KD in adults are still lacking.[22,23] We reviewed the evidence from randomized controlled trials (RCT) for the efficacy of MAD in adolescents and adults and conducted a meta-analysis to evaluate the efficacy and adverse reactions of the dietary therapy. The primary outcome measure is to evaluate the efficacy of diet therapy in DRE with more than 50% seizure reduction along with other secondary outcome measures including quality of life and adverse events.

As varying studies were reporting the different proportion of epileptic patients getting benefit from the MAD therapy. Hence, to get a clear picture of the effect of the MAD diet on DRE subjects, present systematic review and meta-analysis was conducted of RCT, to get a pooled estimate.

Methods and materials

Design

This systematic review adhered to the preferred reporting items for systematic reviews and meta-analysis and followed a prior defined unpublished protocol. Our protocol has been registered on PROSPERO. The registration number is (CRD42022290996).

Search strategy

An online literature search was performed by three investigators independently by using three databases PubMed, Embase, and Cochrane Library since inception till 31 January 2023. The keywords used for searching literature in the above-mentioned database were "Diet" OR/AND "Ketogenic Diet" OR/AND "Modified Atkins diet" OR/AND "MCT" OR/AND "Medium Chain Triglyceride" OR/AND "MAD" OR\AND "KD" OR\AND "LGIT" OR\AND "Low Glycaemic Index Treatment" OR\AND "Epilepsy" OR\AND "convulsions" OR\AND "Seizures" OR\AND "RCTs" OR\AND "RCT" or combinations of these terms.

Selection criteria: the eligibility criteria for including studies in meta-analysis was as follows: 1) population, patients with DRE; 2) intervention, the MAD therapy given to DRE patients; 3) comparator, the DRE patients not receiving MAD diet as treatment; and 4) study design, only RCTs evaluating efficacy of MAD diet in controlling epileptic seizures. Similarly, studies were excluded when: 1) full text was not available; 2) study design other than RCTs; and 3) studies publish in other language then English or whose English translation are not available. A Preferred Reporting Items for Systematic

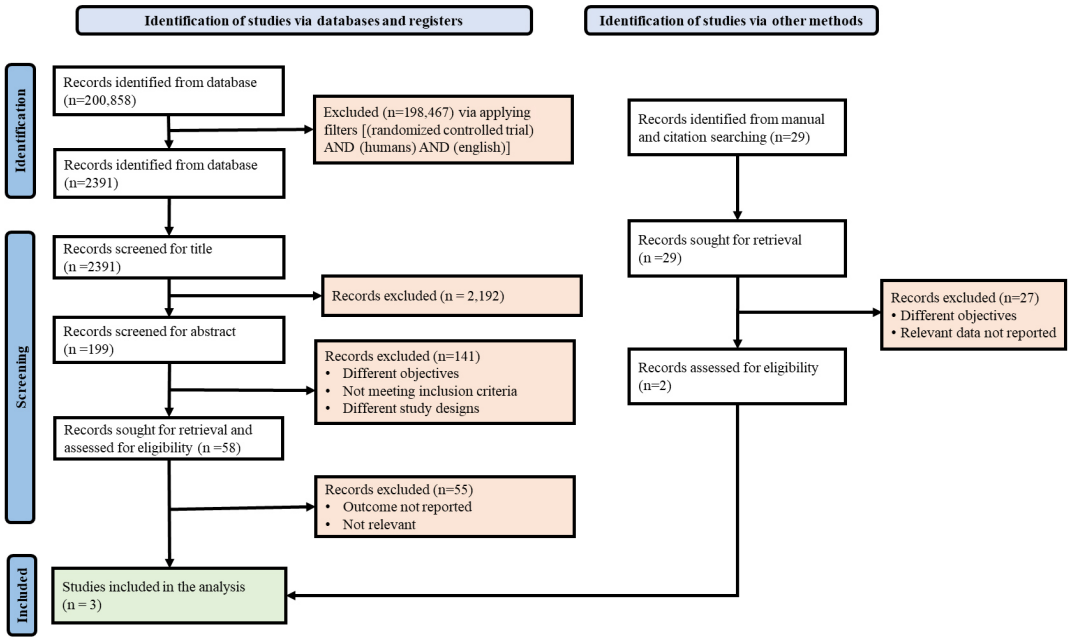

Figure 1. PRISMA flow chart for selection of studies in systematic review and meta-analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Reviews and Meta-Analysis (PRISMA) flow chart of the searching, identification, and selection of the studies is depicted in Fig. 1.

Outcome

The proportion of reduction in seizures in epileptic patients receiving the MAD treatment was one of the outcomes of interest. Also, the relative risk reporting the relationship of reduction of seizure and MAD treatment in RCTs was checked. Additionally, the data used to calculate these two measures (proportion and relative risk) were also considered as an outcome.

Data extraction

Three investigators independently screened the articles from the above-mentioned databases & extracted data from studies included for meta-analysis. The appropriateness of the data was checked by corresponding author. Any discrepancies were resolved by discussing the issues with the corresponding author. Data regarding: surname of author and year of publication of study, study design followed, site of patient's enrolment, target age group of patients, number of participants in treatment and comparator arm, the diagnosis of patients, type of seizures experienced, type of intervention/dietary therapy induced, duration of study, dose of treatment, and comparison treatment used were extracted and maintained in a standard file.

Quality of studies

The two authors' independently reviewed the included articles to estimate Jadad score, and any disagreement was resolved by corresponding author. Jadad score was used to assess the methodological quality of randomized clinical trials. In this respective score, scoring is done according to the presence of three domains features in methodological features first randomization, second blinding, and third accountability of all patients.

Statistical analysis

A meta-analysis to estimate the overall effect of MAD in DRE patients was performed. The pooled summary effect (proportion and risk ratio [RR] with its respective 95% confidence interval [CI]) was computed using the fixed-effect model or random-effect-model. The Q-statistics and I^2-statistics was used to estimate heterogeneity in effect size across all the studies. The effect sizes in meta-analysis vary from study to study, therefore identifying these effect sizes and quantifying this heterogeneity is an important point to be considered. The Q-statistics examine the presence or absence of heterogeneity across studies, whereas I^2-statistic describes the percentage of variation across studies that are due to real heterogeneity rather than chance alone. Based on these two measures of heterogeneity (Q and I^2), the appropriate model (fixed effect model and random effect model) was selected to generate pooled effect size. If the degree of heterogeneity in effect size was significantly high (i.e., I^2 >30%) random effect model was used; otherwise, fixed effect model is used.[24] Forest plot was made to display the result of individual included studies along with their 95% CI and pooled effect size with its 95% CI is also displayed at the bottom of the graph. The publication bias assessment was done by funnel plot (the graphical method) and Begg's test (mathematical method), both. The "meta" package was used to estimate all effect sizes and construction of all the plots in current investigation from the R-Studio version 4.3.1. (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of study

A total of 200,858 articles were retrieved during the search strategy. After applying filters as RCT, humans and studies published in language English only, a total of 2,391 articles were retrieved. 2,192 articles were removed on the basis on title screening followed by abstract screening for 199 articles. Further 141 articles were removed after the abstract screening and finally 58 articles were assessed for full text assessment. At last, only three studies were included in the meta-analysis, following a stringent inclusion criterion, in which a reduction in seizure by use of MAD was reported as proportion and RR. The flow of literature search is displayed in PRISMA flow chart (Fig. 1). The characteristics of all three RCTs included in meta-analysis is given in Table 1.

In the present investigation, two meta-analyses were performed. First, the proportion was taken as effect size for a reduction in seizures by ≥50% in epileptic patients. Second, the (relative risk) RR was taken as the effect size for a reduction in seizure by ≥50%. For reduction in seizure ≥50%, only three studies have provided both effect sizes (proportion and RR). Therefore, three studies were included in meta-analyses.

Table 1. Characteristics of the studies included in the meta-analysis

Study	Study design	Site of patient's recruitment	Target group	Number of participants in two arms of RCT		Diagnosis	Seizure type	Type of dietary therapy	Duration of Intervention (months)	CHO (g)	Comparator/ standard treatment	Jadad score
				Intervention	Control							
Zare et al. (2017)[22]	RCT	Adult Neurology Clinic of Kashani Hospital	Adult	34	32	DRE	Complex partial, generalized tonic clonic	MAD	2	15	ASM	3
Kverneland et al. (2018)[26]	2-armed, open RCT	National Centre for epilepsy, a tertiary referral centre in Norway	Adult	28	34	DRE	Focal	MAD	3	16	Habitual diet	3
Manral et al. (2023)[25]	Prospective randomized open-label, blinded end-point controlled trial with two parallel arms design	Neurology OPD AIIMS, New Delhi, India	Adolescents and adults	80	80	DRE	Tonic, atonic, focal seizures, generalized tonic-clonic, seizures, myoclonic jerks, multiple seizure types	MAD	6	20	Normal diet	3

RCT, randomized controlled trial; CHO, carbohydrate; DRE, drug resistant epilepsy; MAD, modified Atkins diet; ASM, anti-seizure medication; OPD, outpatient department.

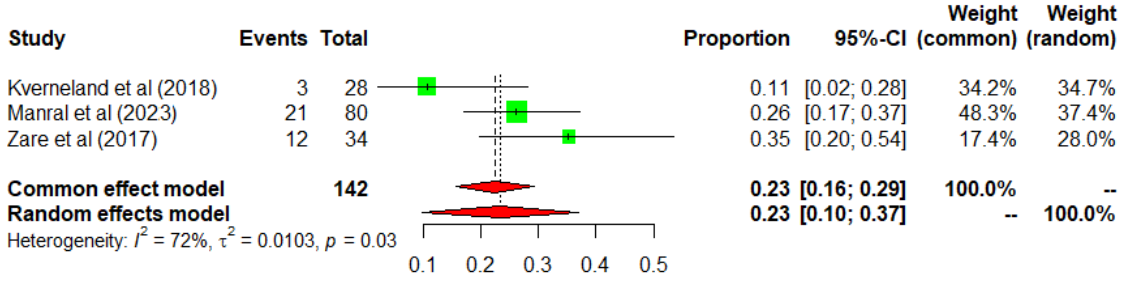

Figure 2. Forest plot with each study effect size (proportion) and summary effect size ≥50% reduction in seizure. CI, confidence interval.

Meta-analysis of proportion for a reduction in seizure ≥50%

The heterogeneity in effect size across the three studies was statistically significant (Q-value=7.08; *p*-value=0.02). The degree of heterogeneity was I^2=71.8% (95% CI, 4.4% to 91.7%, hence the random-effect model was used to estimate pooled proportion. The forest plot (Fig. 2) represents the results of this meta-analysis. The individual proportion obtained by three studies was Zare et al.[22] (prop, 0.35 [0.20-0.54]), Kverneland et al.[23] (prop, 0.11 [0.02-0.28]), and Manral et al.[25] (prop, 0.26 [0.17-0.37]). The pooled proportion was 0.23 (95% CI, 0.10-0.37). The highest weight was obtained by the study Manral et al.[25] (37.4%) and lowest weight was obtained by study Zare et al.[22] (28.0%). The funnel plot (Fig. 3) shows one study of inverted funnel hence, publication bias was present. Begg test shows statistically insignificant result for publication bias (*p*-value=0.60).

Meta-analysis of relative risk for a reduction in seizure ≥50%

The heterogeneity in effect size across the three studies was statisti-

cally insignificant (Q-value=3.36; *p*-value=0.18) and the degree of heterogeneity was I^2=40.6% (95% CI, 0.0% to 81.8%). Hence, random-effect model was used to estimate the pooled relative risk. The forest plot (Fig. 4) represents the results of this meta-analysis. The individual relative risk obtained by three studies was Zare et al.[22] (RR, 23.55 [1.45-381.82]), Kverneland et al.[23] (RR, 1.82 [0.33-10.15]), and Manral et al.[25] (RR, 10.50 [2.55-43.31]). The pooled relative risk using the random effect model was 6.47 (1.60-26.14) which was statistically significant (*p*-value <0.05). The highest weight was obtained by the study Manral et al.[25] (43.3%) and the lowest weight was obtained by Zare et al.[22] (19.2%). The funnel plot (Fig. 5) shows absence of publication bias, as all the studies are inside inverted funnel. Begg test shows statistically insignificant result for publication bias (*p*-value=0.60).

Quality of studies included for meta-analysis

All three studies[22,25,26] included for meta-analysis were given 3 Jadad scores, therefore these studies come under a high-quality domain i.e., low risk of bias. For randomization, method of randomization, and accountability of subject's columns, all three studies were given maximum points, but none of the three studies practiced the method of double-blinding, therefore the studies were given no score for this column. The result of the Jadad score is shown in Table 1.

Discussion

Two meta-analyses addressing the efficacy of the KD in adults have been published. Liu et al.[13] in 2018 conducted meta-analysis including observational studies of KD in adults, reported combined efficacy rates of all the symptoms of seizure freedom, seizure reduction by 50% or more, and seizure reduction below 50% in adults with intractable epilepsy were 13%, 53%, and 27%, respectively. Another meta-analysis published in 2015 evaluated 12 studies, the responder rate ranged from 13-70%.[27] The subgroup analysis was done according to the type of KD, with a combined responder rate of 52% for classical ketogenic diet (CKD) and 34% for the MAD. In addition, one Cochrane systematic reviews on Ketogenic diet for DRE published

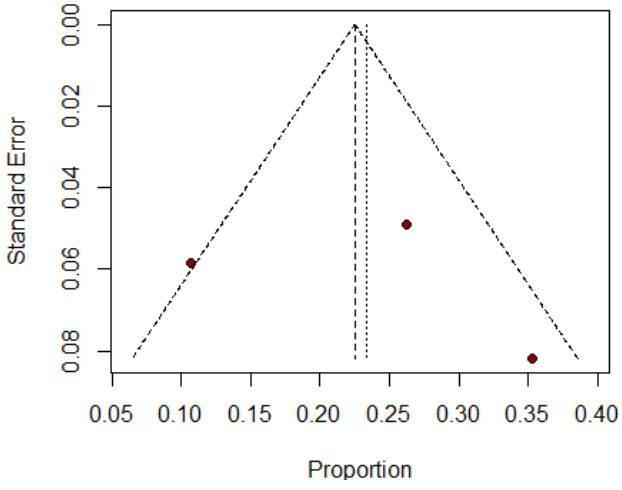

Figure 3. Funnel plot of studies using proportion as effect size in ≥50% reduction in seizure.

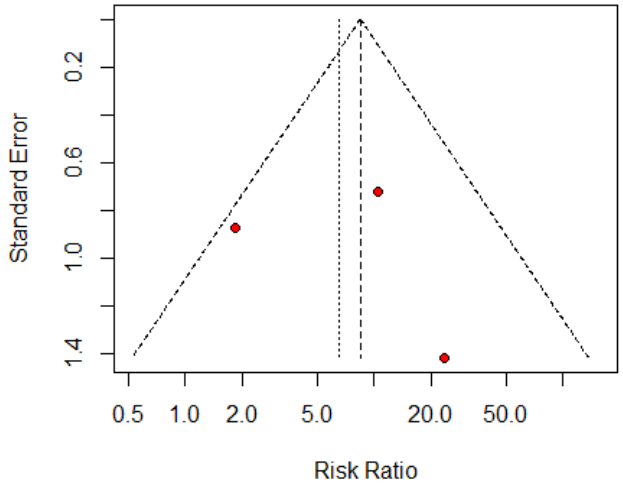

Figure 5. Funnel plot of studies using relative risk as effect size in ≥50% reduction in seizure.

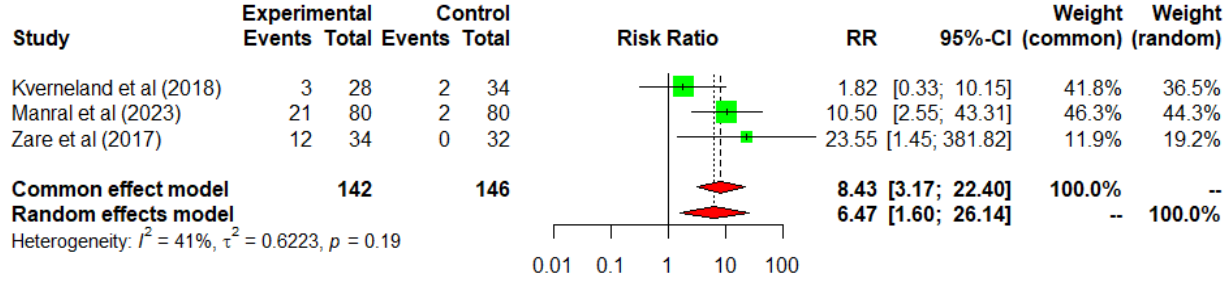

Figure 4. Forest plot of each study effect size (relative risk) and summary effect size ≥50% reduction in seizure. RR, risk ratio; CI, confidence interval.

concluded that more palatable but related diets, such as the MAD, may have a similar effect on seizure control as the classical KD, but could be associated with fewer adverse effects. For people who have drug-resistant epilepsy or who are unsuitable for surgical intervention, KDs remain a valid option. Further research is required, particularly for adults with drug-resistant epilepsy.[10] In adults, including two RCT's[22,26] no participants experienced seizure freedom. Seizure reduction favored KDs (MAD only) over usual care reported (RR, 5.03, 95% CI, 0.26 to 97.68, p=0.29; two studies, 141 participants; very low-certainty evidence). Our study concentrated on those RCTs that included a true standard care of treatment to evaluate the effect of a dietary intervention compared with no intervention at all. Hence, studies comparing two types of KDs were beyond the scope of this review.

However, no meta-analysis has been done to compare the efficacy of MAD along with standard drug therapy to stanadrad drug therapy alone in reducing the seizure frequency and psychological outcomes at 6 months in adolescence and adult in non-surgical patients of DRE and our study is the first up to the best of our knowledge.

In current investigation, the reduction in seizures ≥50% were 0.23 of the total proportion of DRE patients. Publication bias was observed by the graphical method, but not by mathematical method. Additionally, a statistically significant pooled RR suggests that the MAD group will be 6.47 times more prone to the reduction of seizures ≥50%. Publication bias was not observed by both methods (graphical or mathematical).

To have a better understanding of the MAD for seizure reduction in subjects with epilepsy, the following conjectures can be made. First, the authors cannot rule out that the treatment response are poor in people with PWE, having longer seizure history as compared to people with PWE having shorter seizure history.[26] Second, Klein et al.[28] and Kossoff et al.[29] suggested that the efficacy of MAD was observed after a few weeks or up to 2 months of treatment, but 12 week on diet may still be shorter to detect reduction in seizure frequency. Kverneland et al.[26] observed the reduction in seizure frequency and severity after 2 and 3 months for three subjects. Therefore, this was important to see the effect of the duration of diet intervention. Third, when a comparison was done between the CKD and MAD, the former was better for children and adults because of the Ketogenic ratio of 2.5-4.[30] Fourth, there were few subjects with focal epilepsy in the study because of the exclusion of surgically remediable causes of epilepsy. Subjects with surgically treatable focal epilepsy do not respond well to a Ketogenic diet.[31] Fifth, no relationship was found between age, sex, seizure types, epilepsy syndromes, co-morbid cerebral palsy, maternal literacy, vegetarianism, urinary ketosis and seizure control, and urinary ketosis and seizure control.[20] Freeman et al.[32] suggested a lack of differences in seizure control based on age, sex, seizure type, or seizure frequency demonstrated in a prospective study on a Ketogenic diet. Sixth, MAD could be successfully administered, feasible and acceptable by subjects with low-level literacy as compared to MAD.[25] The counselling time was also higher, 2-3 hours, compared to 30-45 minutes in an earlier version of MAD.[19] MAD side effects are well managed with medical measures and reassurance therefore did not require discontinuation of the diet. Seventh, retention appeared higher on MAD than on KD, so more tolerate regimens may be proposed as feasible treatment for older people. More than 50% of the patients were motivated to maintain it as long as seizures were reduced.[33,34]

This meta-analysis should be interpreted in light of certain limitations. First, blinding was not done in any study selected for meta-analysis which increases the bias in the RCT. Second, studies included in the meta-analysis are less in number (only 3) and short duration of follow up, different distributions of age, gender, seizure type, and other uncontrolled confounding factors might add to the bias of the meta-analysis. More studies having the same objective are required. Third, stratification by age, sex, seizure types, epilepsy syndromes, co-morbid cerebral palsy, maternal literacy, vegetarianism, and urinary ketosis should be done in further RCT to get a clearer picture of scenario.[32] Fourth, subgroup meta-analysis and meta-regression was not advisable as the studies were fewer in number.

The present meta-analysis has few strengths. The literature search strategy was rigorous and the research question was supported by clear eligibility criteria, each step in the review was done by multiple reviewers to ensure accuracy, preferred reporting items of systematic review and meta-analysis during the preparation of the manuscript was followed and meta-analysis was conducted adhering to guidelines Cochrane Handbook of systematic review and meta-analysis.

Implication for research

The less restrictive and more liberal forms of diet therapy are effective, relatively safe, and tolerable dietary treatment for adults and young children with refractory epilepsy. The mechanism of action of diet therapy, especially at the cellular and molecular levels, in different types of diseases, is poorly understood. Recent studies have shown that gut microbiota plays an important role in the anti-seizure effects of KD. Therefore in-depth investigations into the intrinsic ther-

apeutic mechanism of the KD in different decreases are needed, as it will not only provide insights into the disease pathogenesis from a new perspective, but also lead to the identification of key intermediate biochemical pathways, molecular, and/or other factors, such as gut microbiota, that governs the KD treatment-related effects, and these can be utilized as promising targets for drug design discover novel targets for therapeutic, to create clinical formulations of the KD, and to determine if certain types of fats and ketogenic ratios relate to the clinical efficacy. High-quality RCTs must be conducted with a large number of patients and well-defined outcomes. In addition, future trials should validate potential biomarkers, including the assessment of serum parameters (adenosine and ketones) and/or the gut microbiome.

Conclusion

Modified Atkins diet therapy was efficacious, feasible, well-tolerated, and had better compliance along with seizure reduction in adolescents and adults with DRE. KD and its variants should be considered as an alternative for non-surgical DRE, of any age. Each patient must have an individually customised diet; however, adults have more difficulty in maintaining CKD. Future studies would be needed to identify neurophysiological and genetic biomarkers associated with a MAD response that may have implications for clinical care by encouraging targeted and earlier use of the MAD and also individualized risk-benefit analysis of therapeutic diet, which provided alternative therapy to standard-care treatment.

Conflict of Interest

Authors declare no conflict of interest.

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