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Do certain subpopulations of adults with drug-resistant epilepsy respond better to modified ketogenic diet treatments? Evaluation based on prior resective surgery, type of epilepsy, imaging abnormalities, and vagal nerve stimulation

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ABSTRACT

Objective: Adults with drug-resistant epilepsy (DRE) are among the most challenging to treat. This study assessed whether specific subpopulations of adult patients with refractory epilepsy responded differently to modified ketogenic diet (MKD) therapy.
Methods: Changes in seizure frequency, severity, and quality of life (QOL) were retrospectively analyzed based on pre-MKD surgical history, type of epilepsy, imaging findings, and vagal nerve stimulation (VNS) history among adults, ≥17 years of age, with DRE, receiving MKD therapy for three months. Additionally, particular attention was made to medication and VNS adjustments.
Results: Responder rates in seizure frequency, severity, and QOL reported among those with prior surgery were 56%, 75%, and 94%, respectively. Among those with focal epilepsy: 57%, 76%, and 76% had improvements in seizure frequency, seizure severity, and QOL, respectively whereas 83% improvement was seen for all three measures in those with generalized epilepsy. Among those with abnormal imaging: just over 50% reported improvements on all measures. For those with VNS, 53%, 63%, and 95% had improvements in seizure frequency, seizure severity, and QOL, respectively. No statistical differences in seizure frequency, severity, or QOL were noted between groups based on prediet surgical history, seizure type, imaging abnormalities, or VNS history. Compared with expected improvement from medication adjustment alone, significant improvement was seen for all groups; notably, the Z-test for proportions for the surgery group, when compared with placebo responder rates at 20%, was 3.6, $p < 0.001$.
Conclusions: Modified ketogenic diet therapies are effective in improving seizure frequency, severity, and QOL and may offer the best chance for improvement among those whose seizures have persisted despite surgical intervention and VNS therapy. All types of epilepsy respond to MKDs, and possibly those with generalized epilepsy may respond better.

1. Introduction

Current treatment options for individuals with drug-resistant epilepsy (DRE) include surgery, laser interstitial thermal therapy (LITT), vagal nerve stimulation (VNS), responsive neurostimulation (RNS), deep brain stimulation (DBS), dietary therapy, and further medication trials. To achieve seizure freedom, high doses of antiepileptic drugs (AEDs) are often prescribed, though after two failed medications, success of achieving seizure freedom is only 5–10% [1–4]. Surgical options are frequently contemplated (though often later than is ideal), and dietary treatments are rarely considered at all in adults, despite the evidence of their efficacy with improved feasibility of modified forms. While the first mention in the literature of ketogenic diets (KDs) for epilepsy dates to the 1920s [5,6], renewed interest in the past few decades in the classic ketogenic and modified ketogenic diets (MKDs) has only more recently meant that research is showing just how efficacious these diets can be. These diets include the modified Atkins diet (MAD), low glycemic index treatment (LGIT), medium chain triglyceride (MCT) diet, and the Modified Ketogenic Diet (in which carbohydrates, protein, and fat are individualized). The use of KD therapies has demonstrated efficacy in reducing seizure frequency by ≥50% in 45% of adults following KDs and MKDs [7,8], with a recent meta-

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analysis showing a reduction by ≥50% in 53% of adults [9]. Additionally, two randomized controlled trials showed the efficacy of these diets, though to a lesser extent than prior trials, with Zare et al. finding ≥50% reduction in seizure frequency in 35.3% of adults on MAD and with Kverneland et al. finding a >25% improvement (though not a >50% improvement) in seizure frequency among those who completed the therapy [10,11]. Compliance has been an issue frequently cited, but a recent study found that supplementation with ketogenic formula while on the MAD increased the chance patients remained on the diet [12]. Additionally, despite the perceived restrictiveness of the diet, patients generally report improvement in quality of life (QOL) [13–15]. While researchers have demonstrated the effectiveness of MKDs, there is a paucity of evidence on whether any subpopulations of patients with epilepsy respond more or less favorably to these diets.

To our knowledge, there is no literature comparing response rates to KD therapies among patients who have had intracranial surgery and those who have not had surgery. While postsurgical patients were included in prior studies, for example, as evidence by a chart in a paper by Kverneland et al. [10], they did not evaluate if this postsurgical population had a different response rate to MKD therapy than those who did not have surgery. There is also very little literature evaluating MKDs in focal versus generalized epilepsy. The efficacy of MKDs for reducing seizure frequency among those with specific syndromes—including Dravet syndrome [16,17], Lennox–Gastaut syndrome [18,19], and juvenile myoclonic epilepsy (JME) [20], has been reported, but these studies lacked comparison groups. Only two studies compared focal with generalized epilepsy in adults [21,22]. Sirven et al. reported similar efficacy across all seizure subtypes—but the study was small (only 7 at follow-up) [21]. The other study by Nei et al. evaluated the classic KD and noted a nonsignificant trend toward those with symptomatic generalized epilepsy responding better than those with focal epilepsy [22].

Studies evaluating structural etiologies were small and few but found what they felt was a surprising improvement in children with structural intracranial injuries [23,24]. To our knowledge, only one study has evaluated patients who received concurrent VNS therapy and ketogenic dietary therapy [25]. Half of these patients were implanted and had significant VNS adjustments during the study period, as they evaluated whether the addition of VNS to the diet improved seizures [25]. To our knowledge, the efficacy of MKD therapy among those who had VNS, but still had persistent seizures, has not been evaluated. Finally, prior studies nearly universally fail to account for medication adjustments or VNS changes made concurrent to MKD treatment, which can be seen as a major confounder.

A better understanding of which populations may best respond to MKD therapies and evaluation of medication or VNS adjustments would be highly useful in clinical practice. This study examines the response to MKD therapy among patients who have had prior surgery for epilepsy or have had prior VNS placement. Additionally, whether the response to MKD therapy varies between those with focal verses generalized epilepsy was evaluated. And finally, whether the response to MKD therapy varies between patients whose brains are structurally abnormal verses patients with normal brain imaging was evaluated.

2. Material and methods

This study was approved by the Institutional Review Board of Rush University Medical Center. Data for this retrospective study were obtained from an ongoing quality improvement initiative at the Clinic for Dietary Treatments of Epilepsy at the Rush Epilepsy Center.

2.1. Patients

Adults (≥17 years) with DRE, with baseline and approximately three-month follow-up appointments between October 2012 and April 2016, who were deemed compliant with the MKD based on diet recalls, were included.

Prior to starting an MKD, all patients attended a group education class and then were seen individually by both the registered dietitian nutritionist (RDN) and epileptologist after this group session (baseline visit) and again individually at about three months (range: 2–7 months). Patients received personalized MKD goals from the RDN at the initial visit. Modified ketogenic diet education targeted 15 g net carbohydrate (MKD-15) and 50 g net carbohydrate (MKD-50) versions of the diet, each with personalized protein (1 g/kg dosing weight using either actual or adjusted weight using a 25% adjustment factor) and fat goals. Both protein and fat goals were provided in grams per day, as well as standard household measurement techniques for ease of understanding. The patient's ability to comply, as well as the severity of their epilepsy, were considered by the treatment team when determining which diet to initiate.

Compliance was determined based on 24-hour diet recalls by the RDN, excluding those with daily consumption of ≥75 g net carbohydrates. Noncompliance (≥75 g net carbohydrate per day) was chosen based on a 25% leeway on the upper end of LGIT therapy allowing for 60 g total carbohydrate daily [26].

2.2. Outcome measures

Data obtained at baseline and three-month follow-up visits included the following: demographics (gender, race, age), seizure frequency, seizure severity, and QOL. The following were obtained from chart review and/or confirmation with the patient/family at the same time points: history of epilepsy surgery, seizure type, Magnetic Resonance Imaging/Computed Tomography (MRI/CT) imaging findings, history of vagus nerve stimulator (VNS) placement prior to MKD, any VNS setting changes made during MKD therapy, AED type and dose, and any changes to medication type or dosing made during the MKD therapy period. Diet compliance was based on 24-hour recalls performed by the RDN.

Treatment outcomes assessed at pre-MKD baseline and after three months of MKD included self-reported 1) change in seizure frequency (defined as ≥50% improvement), 2) improvement in seizure severity (defined as decrease in duration or intensity), and 3) improvement in QOL (defined as improvement in mood, alertness, memory, sleep, and/or attention).

The variables of interest included the following: 1) prior intracranial surgery and type, 2) primary seizure type (defined as focal/multifocal or generalized, determined clinically based on seizure semiology and supported by electroencephalogram (EEG) results when available), 3) presence of abnormal imaging prior to MKD (defined as any finding other than chronic microvascular changes or mild diffuse atrophy as determined by reviewing MRI/CT reports when available), and 4) presence of VNS (with attention paid to how long it was placed prediet initiation and if any VNS setting changes were made during the 3-month trial period or shortly before the trial period). For those who had surgery, the imaging data that were used were presurgery imaging findings.

2.3. Statistical analysis

Outcome measures including improvement in seizure frequency, seizure severity, and QOL were evaluated based on surgery history, seizure type, VNS history, VNS adjustments, and AED adjustments during the study period with Chi-square test or Fisher's exact test. One-sample Z-test was used to compare the outcome measures of each of the groups with the improvement expected of continued medication adjustment alone (while this has been shown to be about 5–10% [1–4], given placebo effects in recent drug trials were 20% [27,28], we set this at 20%). All statistical analyses were performed with SAS 9.4 (SAS Institute Inc., Cary NC, USA). A p-value < 0.05 was considered significant.

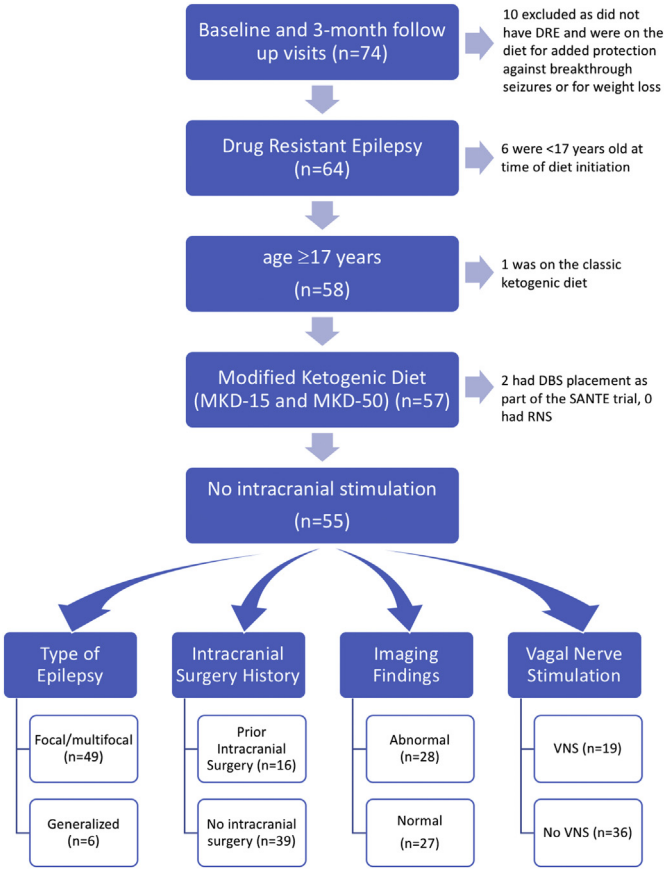

Fig. 1. Exclusion chart among adults with medically intractable epilepsy following modified ketogenic diet (MKD) therapy. DBS: deep brain stimulator; RNS: responsive nerve stimulator; SANTE trial: Stimulation of the Anterior Nucleus of the Thalamus; MKD-15; modified ketogenic diet—15 g net carbohydrate; MKD-50: modified ketogenic diet—50 g net carbohydrate.

3. Results

A total of 74 patients were seen at baseline and follow-up visits, 55 of which met inclusion criteria; Fig. 1. The sample was primarily white (74%), female (73%), with a mean age of 38 years (range: 17–70 years). Time on the diet at study follow-up period ranged from two to seven months. There were no significant differences in proportion of patients with ≥50% improvement in seizure frequency based on MKD type (MKD-15 versus MKD-50). Improvements in seizure frequency, severity, and QOL for the entire population as well as more detailed discussion about diet type, and side effects of MKD therapy are reported in a companion paper [29].

A total of 29% (n = 16) of patients had undergone intracranial surgical intervention procedures prior to MKD (Table 1) with a median time since surgery of 15.5 years (range: <1–35 years, interquartile range (IQR): 11). The majority of patients had focal epilepsy identified as the primary seizure type. Nearly 50% had documented abnormal brain imaging prior to starting MKD. Approximately one-third had VNS placement prior to MKD therapy, with a median time since implantation of 6 years (range: 0–29, IQR: 9); Table 1.

3.1. Surgical history outcomes

A total of 56% of those who had undergone surgical intervention prior to MKD therapy reported ≥50% improvement in seizure frequency after 3 months of MKD; Table 1. Compared with typical placebo responder rates in drug studies (set at 20%) [27,28], the surgery group had significantly higher proportion of patients with improvement (56%, z-value = 3.6, p-value < 0.001). No statistically significant differences in seizure frequency, severity, or QOL were found between those who had and had not undergone surgical intervention prior to MKD therapy; however, the majority of those who had undergone surgical intervention reported reduction in all three outcomes; Table 1.

3.2. Seizure type outcomes

A total of 83% (n = 5) of patients with generalized epilepsy had ≥50% improvement in seizure frequency while 57% (n = 28) of patients with focal epilepsy had ≥50% improvement in seizure frequency. Compared with expected improvement from continued medication adjustment alone (set at 20%), both the group with generalized epilepsy (83%, z-value = 6.5, p-value < 0.001) and the group with focal epilepsy (57%, z-value = 3.88, p-value < 0.001) had significantly higher proportions in improvement. There were no significant differences in proportion of patients with ≥50% improvement in seizure frequency, severity, or QOL based on seizure type; Table 1.

3.3. Imaging findings outcomes

There were no significant differences in proportion of patients with ≥50% improvement in seizure frequency, severity, or QOL based on brain imaging findings; Table 1.

There were two patients that we were unable to obtain imaging data for prior to their surgical resections and unable to determine

Table 1
Changes in seizure frequency, seizure severity, and quality of life after 3 months of modified ketogenic diet therapy among adults with intractable epilepsy based on surgery, seizure type, imaging findings, and VNS.

		Improvement in seizure frequency			Improvement in seizure severity			Improvement in quality of life		
	Total	<50%	≥50%	p	No	Yes	p	No	Yes	p
Total sample n (%)	55 (100%)	30 (40%)	33 (60%)	–	13 (24%)	42 (76%)	–	7 (13%)	48 (87%)	–
Surgery n (%)										
Intervention*	16 (29%)	7 (44%)	9 (56%)	0.72	4 (25%)	12 (75%)	1.0	1 (6%)	15 (94%)	0.66
None	39 (71%)	15 (38%)	24 (62%)		9 (23%)	30 (77%)		6 (15%)	33 (85%)	
Seizure type n (%)										
Generalized	6 (11%)	1 (17%)	5 (83%)	0.38	1 (17%)	5 (83%)		1 (17%)	5 (83%)	0.58
Focal	49 (89%)	21 (44%)	28 (57%)		12 (24%)	37 (76%)	1.0	6 (12%)	43 (88%)	
Imaging n (%)										
Normal	27 (49%)	12 (44%)	15 (56%)	0.46	9 (33%)	18 (67%)	0.06	5 (19%)	22 (81%)	0.42
Abnormal	26 (47%)	9 (35%)	17 (65%)		3 (12%)	23 (88%)		2 (8%)	24 (92%)	
Unavailable	2 (4%)									
VNS n (%)										
Yes	19 (35%)	9 (47%)	10 (53%)	0.42	7 (37%)	12 (63%)	0.11	1 (5%)	18 (95%)	0.40
No	36 (65%)	13 (36%)	23 (64%)		6 (17%)	30 (83%)		6 (17%)	30 (83%)	

*Includes resection or craniotomy; only 3 patients had craniotomy without resection; VNS: vagal nerve stimulator.

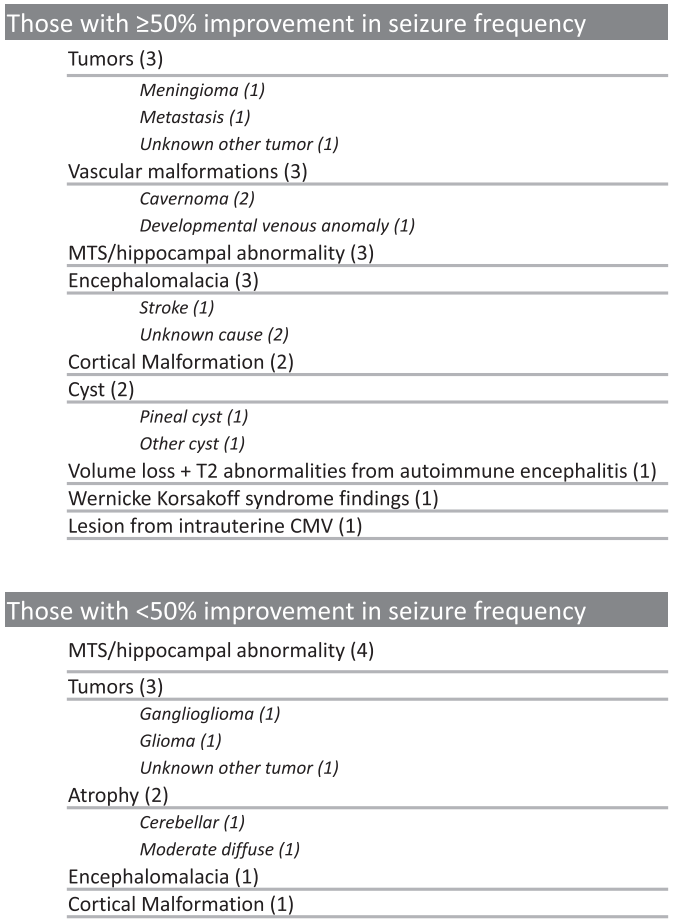

Fig. 2. Imaging abnormalities found on MRI/CT scans of patients with and without ≥50% improvement in seizure frequency. *Several patients had multiple imaging abnormalities. MTS: Mesial Temporal Sclerosis; CMV: Cytomegalovirus; MRI: Magnetic Resonance Imaging; CT: Computed Tomography.

whether the surgeries were done based upon an imaging abnormality or simply on the basis of EEG or semiology findings, so these patients were excluded. Please see Fig. 2 for a list of the imaging abnormalities noted. Of note, several patients had more than one imaging abnormality. There did not appear to be any trend in patients with certain imaging abnormalities showing more or less responsiveness to the diet.

3.4. VNS outcomes

The majority of patients reported improvement in seizure frequency, severity, and QOL; however, results were not statistically different between those with or without VNS placement prior to MKD therapy; Table 1. The VNS was turned on for all except for two patients, where the VNS was placed nine and five years prior to MKD therapy and deemed failed. The VNS settings were optimized prior to MKD therapy in all except for one patient.

3.5. Potential impact of AED adjustments and VNS adjustments on outcomes

Median IQR of AEDs at baseline and follow-up for those with ≥50% improvement in seizure frequency, severity, and QOL did not change between baseline and follow-up visits; Table 2. Additionally, there were no significant differences in percent of patients with changes to the AED number or dose nor those with VNS adjustments during the study period; Table 2. While improvement in seizure frequency was noted in 100% of those (n = 3) with medications added, it was also improved among 60% of those with no additional medications added, and 40% of those where medications were discontinued.

Regarding VNS, only two patients had ≥50% improvement in seizure frequency, when VNS settings were increased during the study period; Table 2. One of these patients had their VNS for two years prior to diet initiation, without significant improvement from VNS, and had one setting increase made during the trial period. The other patient had a new VNS placed during the trial period and their settings up-titrated. This second patient was a part of the follow-up subgroups: no prior resective surgery, focal epilepsy, and abnormal imaging (cyst). Of the patients with <50% improvement in seizure frequency, three had their VNS settings increased. Two of these were standard increases and for one, the battery died, and the VNS was re-titrated up during the trial period.

4. Discussion

This study is the first to our knowledge to report on the following: 1) MKD outcomes in individuals who have continued seizures despite epilepsy surgery compared with those who have not had surgery, 2) MKD outcomes in those with abnormal brain imaging versus normal brain imaging, and 3) control (where possible) or account for medication and VNS adjustments during MKD therapy. Additionally, it adds significantly to the paucity of literature on 1) MKD outcomes with focal versus generalized epilepsy and 2) MKD outcomes in those with or without a VNS.

Among those who had undergone resective epilepsy surgery prior to MKD therapy, a significantly higher proportion (56%) of individuals

Table 2
Effect of medication and VNS adjustments on changes in seizure frequency, seizure severity, and quality of life after 3 months of modified ketogenic diet therapy.

		Improvement in seizure frequency			Improvement in seizure severity			Improvement in quality of life		
	Total	<50%	≥50%	p	No	Yes	p	No	Yes	p
Total sample n (%)	55 (100%)	30 (40%)	33 (60%)	–	13 (24%)	42 (76%)	–	7 (13%)	48 (87%)	–
Median number of AEDs n (IQR)										
Baseline	3 (2)	3 (2)	3 (2)	0.95	3 (2)	3 (2)	0.80	2 (1)	3 (2)	0.06
Follow-up	3 (2)	3 (1)	3 (2)	0.69	3 (2)	3 (2)	0.86	2 (2)	3 (2)	0.04
AED number change n (%)										
None	47 (85%)	19 (40%)	28 (60%)	0.30	12 (26%)	35 (74%)	1.0	6 (13%)	41 (87%)	0.69
Added med	3 (5%)	0 (0%)	3 (100%)		0 (0%)	3 (100%)		0 (0%)	3 (100%)	
Discontinued med	5 (10%)	3 (60%)	2 (40%)		1 (20%)	4 (80%)		1 (20%)	4 (80%)	
AED dose change n (%)										
None	35 (64%)	16 (46%)	19 (54%)	0.53	9 (26%)	26 (74%)	1.0	6 (17%)	29 (83%)	0.70
Increased	15 (27%)	5 (33%)	10 (67%)		3 (20%)	12 (80%)		1 (7%)	14 (93%)	
Decreased	5 (9%)	1 (20%)	4 (80%)		1 (20%)	4 (80%)		0 (10%)	5 (100%)	
VNS adjusted n (%) (n = 19)										
Yes	5 (28%)	3 (60%)	2 (40%)	0.61	3 (60%)	2 (40%)	0.27	1 (20%)	4 (80%)	0.28
No	13 (72%)	5 (38%)	8 (62%)		3 (23%)	10 (77%)		0 (0%)	13 (100%)	

AED: antiepileptic drug; IQR: interquartile range; VNS: vagus nerve stimulator.

were found to have ≥50% improvement in seizure frequency than the ~20% [27,28] expected in drug studies for a placebo rate. While it is possible that some of the effect we report could be attributed to potential late effects of surgery, as it is known that those who undergo resective surgery may have late improvements in seizure control [30], this seems unlikely given that mean time since surgery in the current study was 16 years, and the dramatic improvement seen with MKD therapy was over three months of dietary treatment. No differences were found between those who had or had not undergone surgical intervention prior to MKD therapy. This finding is important, as there are limited options for patients whose seizures have continued despite surgery. Thus, MKD therapy should be considered a highly effective therapy for the most difficult patients to treat—those with medically and surgically refractory epilepsy.

In this study, a total of 83% of the population with generalized and 57% with focal seizure types reported ≥50% improvement in seizure frequency. While no significant differences were noted between seizure types, indicating that MKD therapy is effective for both generalized and focal epilepsy, the number of patients with generalized epilepsy who responded may be clinically relevant. It is possible that statistical significance was not achieved because of our small number of patients with generalized epilepsy. While this warrants further study, given the high percentage of patients with focal epilepsy who improved as well, MKDs should be considered highly efficacious for all types of epilepsy.

No differences were found in the response to MKDs between patients who had abnormal imaging and normal imaging. No literature exists examining response rates to MKDs for those with structural abnormalities versus normal imaging, thus, we felt this negative result was worth reporting.

We found the improvement seen in patient with prior VNS placement exciting. While all patients in our study qualified as having refractory epilepsy, those who have also had VNS placement or surgery are usually more refractory than those whose seizures have solely failed multiple medication trials, though we realize that there are patients who are unwilling to undergo any surgical treatment for their epilepsy, and they may be equally refractory. Others have suggested a synergistic effect between concurrent MKD and VNS therapies [25]; however, we did not specifically evaluate this.

Finally, among the available literature, there is a lack of transparency in medication changes and/or VNS adjustments during MKD therapy. While we believe that most researchers attempt to control these factors as much as possible, given the lack of mention of what changes may have been made, this is potentially a confounding factor in many prior studies, but not in ours. This study is unique in that we tracked medication and VNS changes, so as to remove these as potential confounders. While improvement in seizure frequency was noted in 100% of those ($n = 3$) with medications added, it was also improved among 60% of those with no additional medications added and 40% of those where medications were discontinued. This indicates that the majority of the improvements in seizure frequency during the treatment period occurred without addition of medications. Regarding possible confounding effects due to VNS titrations, as mentioned in the results, only one patient's improvement should potentially be equated to VNS changes (it was a new implantation). Given the number of patients in the study, we felt this patient's inclusion (despite the potential confounding effects) was more beneficial than their exclusion, as three patients without improvement also had their settings increased.

Overall, 60% of patients reported ≥50% improvement in seizure frequency after the first three months of MKD therapy, which is on the upper end of the range compared with previous reports between 30% and 60% [7–11]. This may be because noncompliance was an exclusion criterion in the current study. Additionally, in this study, LGIT and MAD were not used specifically but instead, MKD-15 and MKD-50 with individualized protein and fat goals to offer more guidance. This may have resulted in improved compliance and/or efficacy by preventing excess protein and inadequate fat intake, common misperceptions when following KD therapy, both of which may reduce efficacy of KD therapies by reducing ketosis.

Limitations to the current study are similar to those of most retrospective and KD literature, including small sample size, lack of blinding or randomization, and self-reported data. Blinding is extremely difficult in nutrition-based research for obvious reasons.

5. Conclusions

Given the reduction in seizure frequency when compared with continued medication adjustment alone, MKD therapy should be considered early in the treatment course for all individuals with epilepsy. This study suggests several exciting new findings among different populations of patients with epilepsy. Among those who do not qualify for or whose seizures have persisted despite epilepsy surgery, these diets likely offer the best option for seizure control and improvement in QOL. These diets should be discussed with all patients with medically refractory epilepsy early on, and if the physicians do not have the ability to offer dietary treatments themselves (ex. insufficient knowledge or trained RDN), then referral to a center with these capabilities is recommended. For patients who may be surgical candidates, these diets should be offered concomitant to workup for these more invasive treatments.

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All contributors to the above manuscript are listed as authors.

Declarations of interest

Jessica Falco-Walter and Bichun Ouyang have no conflicts of interest. Kelly Roehl authored an introduction to a ketogenic cookbook and received a one-time contract fee but does not receive royalties, she otherwise has no conflicts of interest. Antoaneta Balabanov is an Advisory board member for SK Life Science as well as an Advisory board member for Nutricia.

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Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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