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Establishing an Adult Epilepsy Diet Center: Experience, efficacy and challenges

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ABSTRACT

Objectives: Over 250 medical centers worldwide offer ketogenic diets to children with epilepsy; however, access to these therapies has been extremely limited for adults until recent years. We examine our 5-year experience creating and implementing a dedicated Adult Epilepsy Diet Center designed to provide adults with epilepsy access to ketogenic diets.

Material and methods: Outpatients seen at the Johns Hopkins Adult Epilepsy Diet Center from August 2010 thru September 2015 age 18 years and older were enrolled in a prospective open-label observational study. Patients that also enrolled in ongoing clinical diet trials were excluded from this study. Participant demographics, diet type, urine and/or serum ketones, laboratory studies, seizure frequency, diet duration, reason for discontinuing diet therapy, and side effects were recorded. A subgroup analysis of participants that met International League Against Epilepsy (ILAE) criteria for drug-resistant epilepsy (DRE) and were treated de novo with a Modified Atkins Diet (MAD) was performed to compare outcomes with the current literature regarding efficacy of other antiseizure treatments for DRE.

Results: Two hundred and twenty-nine adults attended the Adult Epilepsy Diet Center, and 168 met inclusion criteria. Two-thirds (n = 113, 67%) were women with an age range of 18–86 years at the initial visit. Thirty-five participants (21%, n = 133) were already on a therapeutic diet while 79% (n = 133) were naïve to diet therapy at the time of the initial visit. Diet-naïve participants were typically prescribed MAD (n = 130, 98%), unless unable to intake adequate oral nutrition, in which case they were prescribed KD (n = 1) or a combination of oral MAD and ketogenic formula (n = 2). Twenty-nine of 130 (22%) participants prescribed MAD elected not to start or were lost to follow-up, and 101 (78%) began MAD.

A subgroup analysis was performed on one hundred and six participants naïve to diet therapy that met International League Against Epilepsy criteria for DRE, were able to tolerate oral nutrition, and were prescribed a MAD. Relative to the number of enrolled participants who had reliable follow-up results for a given duration (including those that ultimately elected not to start or were later lost to follow-up), at 3 months, 36% of these participants responded (≥50% seizure reduction) to diet therapy, and 16% were seizure-free. At 1 year, 30% responded, and 13% were seizure-free. At 4 years, 21% responded, and 7% were seizure-free.

Hyperlipidemia was the most common side effect (occurring in 39% of screened participants, including those on a therapeutic diet prior to the initial visit). Weight loss was also common (occurring in 19% of all participants treated with a ketogenic diet therapy) yet was often an intended effect.

Significance: This study, the largest series of adults with epilepsy treated with ketogenic diet therapies to date, provides evidence that ketogenic diets may be feasible, effective, and safe long-term in adults, although long-term adherence was limited and further adequately controlled studies are necessary to determine the efficacy of ketogenic diets in the treatment of adults with epilepsy.

1. Introduction

Although ketogenic diets are widely implemented for children (in over 250 medical centers worldwide) with drug-resistant epilepsy (DRE) and certain electroclinical syndromes [1], few epilepsy centers worldwide offer these therapies to adults [2,3]. New antiseizure drugs, devices for neurostimulation, and epilepsy surgery continue to be utilized for refractory epilepsy in the adult population. In addition, diet

Abbreviations: KD, ketogenic diet; MAD, Modified Atkins Diet; AEDC, Adult Epilepsy Diet Center.

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therapies may be perceived as restrictive for adults, especially the Classic (4:1 ratio of fat to carbohydrates and protein grams combined) Ketogenic Diet.

Recently, several circumstances have been identified in which the Classic Ketogenic Diet (KD) and other ketogenic diet therapies (Modified Atkins Diet (MAD) [4,5], Medium-Chain Triglyceride (MCT) Diet [6], and the Low Glycemic Index Treatment (LGIT) [7,8]) may be beneficial for adults. First, children on ketogenic diets transitioning out of pediatric neurology clinics require ongoing care by an adult neurologist and registered dietitian [9]. Second, many adults with DRE carry diagnoses of electroclinical syndromes for which diet treatments have been shown to be effective in childhood such as Rett syndrome [10,11], tuberous sclerosis complex [12], Lennox–Gastaut syndrome [13], and juvenile myoclonic epilepsy [14,15]. Third, adults with drug-resistant focal epilepsy who are surgical candidates but not ready to pursue surgery and adults who are not surgical candidates may be seeking an alternative to trying additional antiseizure drugs. Fourth, many adults wish to reduce antiseizure drugs because of side effects. Finally, recent retrospective studies have shown potential benefit of ketogenic diets in adults with refractory and super-refractory status epilepticus who may require long-term diet treatment after recovery, though prospective randomized trials are needed [2,16,17].

Several case series and reviews suggest that the efficacy of ketogenic diets in adults with epilepsy is comparable with that in children [2,3,18–31]. The largest retrospective study to date of the KD from 1930 reported results in 19 adolescents and 81 adults, including patients with both drug-naïve and drug-resistant seizures, of which 56% "derived benefit" [31]. A more recent prospective study of 12 adults treated with a 3:1 ratio ketogenic diet showed a response rate (≥50% seizure reduction) of 44% at 4 months [18] while another study of 9 adults reported completion of a 12-week diet treatment in only 2 participants; both of whom had a greater than 50% seizure reduction [25]. One prospective study examining the efficacy of the MAD in 30 adults showed that 47% achieved a ≥50% seizure reduction at one and three months and 33% at 6 months [20], and another prospective study of 18 adults reported a 28% responder rate at 6 months [22]. Despite these promising results with regard to efficacy, access to these diets remains limited worldwide, and concerns persist regarding adherence in adults.

Because of increasing demand, we created a multidisciplinary Adult Epilepsy Diet Center (AEDC) in 2010 in order to provide ketogenic diets to adults with epilepsy. The purpose of this study was to determine whether ketogenic diets are a feasible and efficacious treatment option when provided to adults as part of a multidisciplinary, outpatient clinic.

2. Methods and materials

Consecutive patients age 18 years and older seen in the Adult Epilepsy Diet Center (AEDC) at Johns Hopkins Hospital from August 2010 thru September 2015 and not eligible for ongoing clinical diet trials (NCT01796574, NCT01834482, or NCT02426047) were enrolled in this prospective, open-label, observational study. The study was approved by the Johns Hopkins Institutional Review Board. Written consent to participate in the study was obtained by all patients or a legally authorized representative for patients not capable of providing informed consent.

At scheduling, patients were mailed or e-mailed a packet of written instructions including a tracking calendar and were asked to record seizures daily (type and frequency) until the first clinic visit (1 or more months prior to the initial visit) to establish a baseline seizure frequency as part of standard clinical care. Patients already on ketogenic diets at the time of scheduling were also asked to record biweekly urine ketones prior to the initial visit.

At the time of enrollment, participants were scheduled for a 60-minute new-patient clinic visit with an adult epileptologist [MCC], followed by a one-on-one interview with a registered dietitian [BJH]. Medical records were reviewed, and participant interviews were conducted to determine seizure characteristics. Electroencephalography findings and neuroimaging were used to classify seizure types and electroclinical syndromes [32]. Medical records were also reviewed for any evidence of an underlying metabolic disorder that might be contraindicated [33,34] as well as cardiovascular risk factors, history of diabetes, nephrolithiasis, anorexia, pancreatitis, cholecystectomy, osteopenia/osteoporosis, and orthostatic hypotension, and at-risk patients were counseled regarding potential risks of exacerbation or recurrence. Baseline vital signs and laboratory studies were obtained per the AEDC protocol (Table 1).

Participants not already on a form of diet therapy at the time of the first visit and able to tolerate oral nutrition attended a group instructional session (typically 60–90 min) on how to begin and continue a 20 g per day net carbohydrate limit MAD per protocol (Table 1). Increased fat intake was encouraged, but a specific target number of fat grams per day was not prescribed. Participants were provided a manual containing a summary of the materials presented in the teaching session, recommended micronutrient supplements, shopping lists, sample menus, potential side effects and management, recipes, websites, and books for reference (Supplementary material).

Those participants who were unable to tolerate oral nutrition were prescribed a formula-based 4:1 ratio KD. Participants aged 21 years or younger were first started on KD with admission to the Johns Hopkins Pediatric Ketogenic Diet inpatient service (before establishing care in

Table 1
Johns Hopkins Adult Epilepsy Diet Center Modified Atkins Diet protocol.

Prediet
Nutrition evaluation
Height and weight, calculation of body mass index
Three-day food record to calculate prediet caloric intake
Food preferences/practices (ex. religious)/prior diets, allergies, intolerances, aversions
Laboratory evaluations
Comprehensive metabolic panel, complete blood count, fasting lipid profile, vitamin D
Antiepileptic drug levels (if applicable)
Urine calcium, creatinine, human chorionic gonadotropin (premenopausal woman)
Diagnostic studies
EEG/Epilepsy Monitoring Unit evaluation (if diagnosis is unclear)
MRI with epilepsy protocol (if applicable)
Screening for cardio- and cerebrovascular risk factors, history of nephrolithiasis
Prediet calendar of daily seizures, start and end of menses (premenopausal women)
Initiation
Diet prescription
20 g net carbohydrates per day (subtracting fiber) Modified Atkins Diet
Liberal fat intake to satiety
Daily multivitamin, calcium and vitamin D supplement (low carbohydrate brand)
Maintain adequate hydration
Monitoring (documented on a calendar)
Seizures daily
Urine ketones daily until reaching 40 mg/dL, then biweekly
Weights weekly
Start and end of menses (premenopausal women)
Follow-up
Clinic visits at 3 and 6 months then annually
Monitoring
Seizure frequency
Urine ketones
Food records/compliance
BMI changes
Side effects
Laboratory evaluations (annual unless otherwise specified)
Comprehensive metabolic panel, complete blood count, fasting lipid profile (at 3 months and more frequent if elevated)
Antiepileptic drug levels
Vitamin D, zinc, selenium levels, free and total carnitine levels
Diagnostic studies
Renal ultrasound (if nephrolithiasis suspected)
ECG (if history of heart disease)
Carotid ultrasound (if prolonged fasting lipid elevation)
Bone density scan (every 5 years, minimum)

the AEDC), and the diet was introduced over 3 days, beginning with an overnight fast from approximately midnight until 5:00 pm the following day, followed by introduction of a 4:1 ratio ketogenic diet at half estimated calorie needs for 1 day then increased to full calories. Serum glucose levels were monitored every 8 h for the first 24 h, and urine ketone levels were collected every morning of the hospitalization. These participants followed up as an outpatient first in the Pediatric Ketogenic Diet Center then in the AEDC. Participants over age 21 years were started on a KD as an outpatient by beginning at 1/3 estimated calorie needs for 1 day, increasing to 2/3 for 1 day then to full calories. Patients receiving nutrition via the combination of enteral and oral feeding were prescribed a diet consisting of an oral MAD combined with a 4:1 ratio KD to obtain adequate daily caloric intake.

All participants were provided a new tracking calendar and instructed to track seizures daily, urine ketone levels daily until they achieved moderate urinary ketosis (40 mg/dL) then biweekly, and weights weekly. Participants were instructed not to change antiseizure drugs during the first month of treatment unless deemed medically necessary and to inform the study team immediately if changes were made.

Participants returned for 30-minute follow-up visits with the neurologist and then 30-minute visits with the dietitian at a minimum of 3 and 6 months, then annually depending on the diet prescribed, diet duration, response to treatment, adherence, and side effects. Follow-up investigations were consistent with those recommended in prior studies [33] (Table 1).

Descriptive statistics were used to present baseline characteristic and safety data. Participants who met International League Against Epilepsy criteria for DRE [35], who were naïve to diet treatment at the time of the initial visit, and who were prescribed a 20-gram net carbohydrate limit per day MAD were examined further to determine overall diet efficacy. Participants were excluded from this subanalysis if they could not reliably quantify seizure frequency or established care fewer than 3 months before data analysis. Given that this was an uncontrolled, open-label observational study, a final analysis was performed including only those participants with DRE and no antiseizure drug changes for the duration of the study.

Participants were defined as diet "responders" if they had ≥50% seizure reduction from baseline and defined as seizure-free if they had no seizures from the time of initial visit to AEDC to follow-up for patients seen less than 1 year or seizure-free for one year or more for participants followed more than 1 year. Proportions were calculated for all categorical variables, and means or medians, standard deviations, and ranges or interquartile ranges were calculated for all continuous variables.

3. Results

3.1. Participants

From August 2010 to October 2015, 229 patients were seen in the Johns Hopkins Adult Epilepsy Diet Center and 226 agreed to participate (Fig. 1). Only 105 (46%) of the consented participants were residents of the state of Maryland, where the Center was located, and 4 patients (2%) traveled internationally to attend clinic. Fifty-eight participants (25%) enrolled in one of three clinical trials (NCT01796574, NCT01834482, or NCT02426047) examining the ketogenic diet for super-refractory status epilepticus (n = 5), the value of a ketogenic diet formula in combination with the MAD in refractory epilepsy (n = 51), or the effectiveness of medium chain triglycerides as an adjunct to the MAD in catamenial epilepsy (n = 2) and were therefore excluded. Among the remaining 168 participants (Fig. 1, Table 2), 67% were women (n = 113), and the age range was 18 to 86 years (mean age 38 years, SD ± 78). Nine participants were presented in prior publications [9,14,27].

Diagnoses included focal or multifocal epilepsy (n = 110 (66% of 168)), genetic generalized epilepsy (n = 37 (22%); a subset of whom were reported previously [14]), symptomatic generalized epilepsy (n = 15 (9%)), seizures with both generalized and focal features (n = 4 (2%)), and focal and nonepileptic seizures (n = 2 (1%); these participants were able to differentiate and quantify these seizure types, confirmed with inpatient Epilepsy Monitoring Unit evaluation).

Thirty-five participants (21%) were already on diet therapies at the time of the initial visit and not enrolled in ongoing clinical diet trials. The majority (n = 23; 66%) had started a diet independently or with the assistance of an outside neurologist and/or dietitian. Several (n = 9; 26%) were transitioning from the Johns Hopkins Pediatric Ketogenic Diet Center to the AEDC (including one patient with Glucose Transporter Type 1 Deficiency syndrome who began a 3:1 ratio classic ketogenic diet at age 6 years and transitioned to the AEDC at age 20 years), and a subset has been reported in a prior study [9], and a small number (n = 3; 8%) previously participated in a study of the Modified Atkins [20,27] or ketogenic diet [36] and were seeking outpatient follow-up.

Among the 133 participants (79%) that were naïve to diet therapy at the time of the initial visit, 2 (2%) had been on no antiseizure drugs and were seeking diet therapy as an alternative to starting an antiseizure drug, 12 (9%) had tried only one antiseizure drug (including 4 that were on no antiseizure drugs at the first visit because of intolerable side effects), and the remaining 119 participants (89%) had tried 2 or more drugs. Nine participants (7%), 7 of whom had previously tried two or more drugs, were seizure-free and attended clinic with the desire to lower antiseizure drug burden. Ultimately, 112 participants met ILAE criteria for DRE (2 or more drugs tried appropriate for the participant's seizure type at adequate doses with continued seizures) [35], and of these, 106 were able to intake adequate oral nutrition, reliably quantify seizures, and have 3 or more months of follow-up.

3.2. Diet prescriptions

Of 35 participants on ketogenic diets at the time of the initial visit (again, excluding participants enrolled in ongoing diet trials), 22 (63%) were on a MAD, 9 (26%) were on a KD, 3 (8%) were on a combination diet (2 on KD with medium chain triglyceride oil added and one on a combination of an oral MAD and KD enterally), and 1 participant (3%) had eliminated carbohydrates from her diet but was not following a strict ketogenic diet.

One hundred and thirty-three participants were naïve to diet therapy at the initial visit, and 130 (98%) were able to take in oral nutrition and were prescribed MAD. Two participants who were enterally and orally fed were prescribed an oral MAD with 4:1 ketogenic liquid supplements (KetoCal®, Nutricia) to be taken when they were not able to take in oral nutrition (e.g., in the setting of frequent seizures or excessive sedation). One enterally fed participant (no oral nutrition) over the age of 21 years was prescribed a 4:1 ratio ketogenic diet initiated as an outpatient per the AEDC protocol.

3.3. Efficacy and adherence

3.3.1. Patients already on diet therapy at initial visit

Of the 35 participants that were on ketogenic diets prior to the initial visit, 27 (77%) remained on diet therapy throughout the study (combined diet duration including prior to and after the first visit to AEDC ranged from 4 months to 36 years, median 32 months). Six (22%) had a ≥50% seizure reduction (saw additional benefit) since the initial visit but did not achieve seizure freedom, 15 participants (56%) are seizure-free (including 12 (44%) that were seizure-free at the time of the first visit to AEDC), and 6 (17%) have seen no change in their seizure frequency or less than 50% seizure reduction since the initial clinic visit. Eight participants are no longer on a ketogenic diet. Half (n = 4) of those that stopped did not feel that they had adequate benefit and stopped after 5 months, 9 months, 3 years, and 7 years of diet therapy, two were lost to follow-up, one was successfully tapered off of a MAD after 1 year of seizure freedom without seizure recurrence, and one

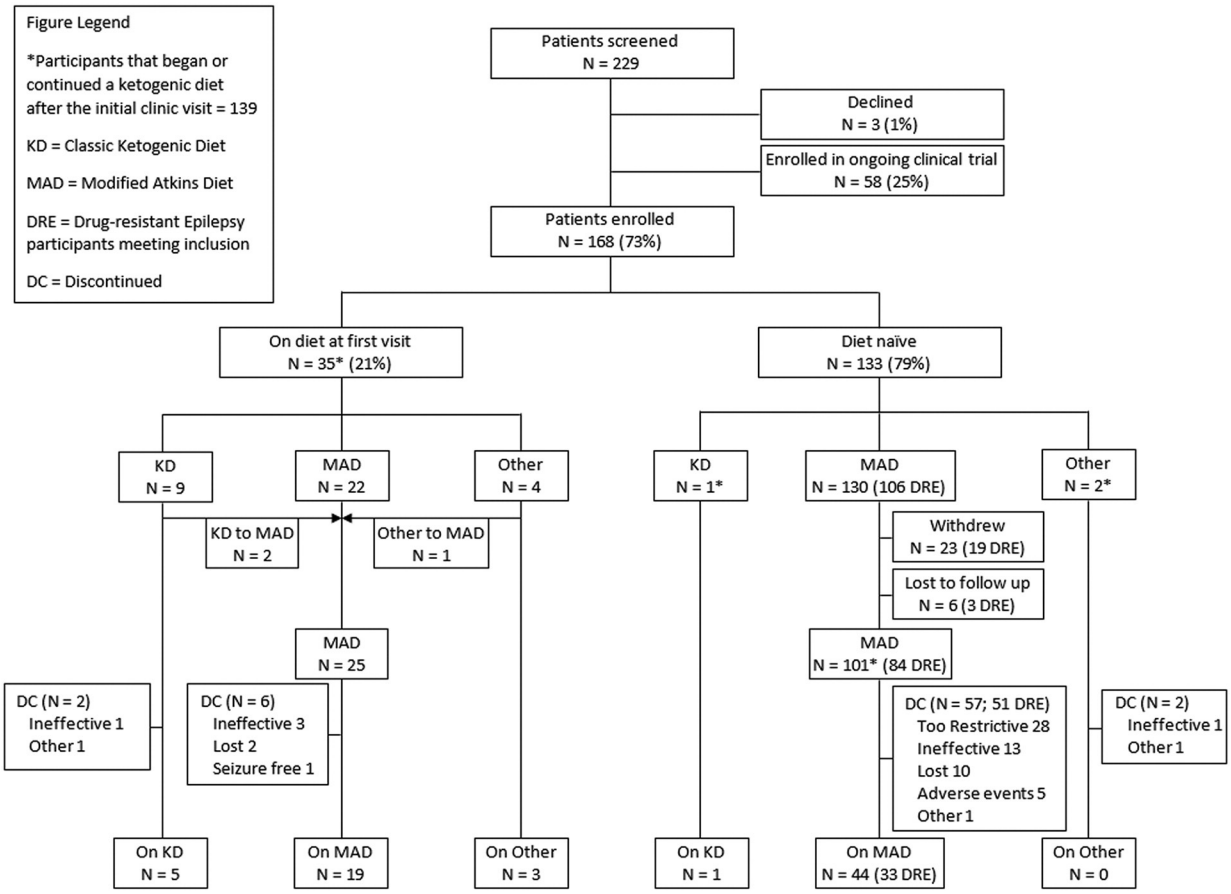

Fig. 1. Participant enrollment.

died of causes deemed unrelated to the ketogenic diet (sudden cardiac arrest related to an underlying metabolic disorder) after 18 years on a classic ketogenic diet.

3.3.2. Patients naïve to diet therapy

One hundred thirty-three participants were naïve to diet therapy at the initial visit (Fig. 1). Three could not intake adequate oral nutrition. Of 130 participants who were introduced to an oral MAD at the time of the initial visit, 101 (78%) actually began MAD, and 29 (22%) elected not to start or never followed up in clinic after the initial visit (Fig. 1). Of the 29 participants that elected not to start, 16 (55%) perceived the diet to be too difficult to follow, 7 (24%) elected instead to pursue antiseizure medication changes, and 6 (21%) were lost to follow-up.

At the time of analysis, 44 (44%) of the original 101 participants that began MAD remain on the diet. Of these, 17 (17%) had a ≥50% seizure reduction but did not achieve seizure freedom, and 22 (22%) became seizure-free. Nine (9%) have seen no change in their seizure frequency or less than 50% seizure reduction since the initial clinic visit, and 57 (56%) have stopped the MAD or were lost to follow-up (Fig. 1).

The diet duration range for the 44 participants still on MAD is 2 months to 5 years (median 25 months, mean 28 months, SD ± 18 months), and the 57 participants that stopped MAD did so between 2 days and 2 years after starting (median 3 months, mean 5 months, SD ± 5 months). Thirty-one participants that stopped MAD (54% of 57) did so by 3 months and 46 (81%) by 6 months. Reasons for stopping included restrictiveness (n = 28; 49%), participants lost to follow-up (n = 10; 18%), inadequate benefit (n = 13; 23%, including 4 with increased seizures), side effects (n = 5; 9%), and unrelated injury (n = 1; 2%). Over half (30 participants; 53%) that decided to stop MAD had a ≥50% seizure reduction when they elected to stop, and 21% (12 participants) were seizure-free from the time that they began MAD (duration 2 days to 23 months, mean 5 months (SD ± 7), median 2 months). Of the 12 seizure-free participants that elected to stop MAD, 11 (92%) found the diet to be too restrictive, and 1 (8%) stopped after an unrelated ankle fracture.

One patient who received nutrition via gastrostomy tube and started the KD as an outpatient remained on the diet throughout the study with >50% seizure reduction. One patient prescribed a combination diet stopped after 4 months because of inefficacy, and the second participant died of Sudden Unexplained Death in Epilepsy (SUDEP) 2 months after initiation of treatment.

Table 2
Patient demographic and clinical characteristics.

	On-diet at first visit (n = 35)	Diet naïve (n = 133)
Gender, female	19 (54%)	94 (71%)
Age, years mean (range)	40 (18–86)	32 (18–70)
Intellectual disability	13 (37%)	27 (20%)
Age, years mean at seizure onset (range)	17 (0–70)	18 (0–83)
# antiepileptic drugs tried, mean (range)	6 (0–17)	6 (0–18)
Seizure frequency per week, median (IQR)	1 (12)	1 (7)
Epilepsy classification		
Localization-related	24 (69%)	86 (65%)
Idiopathic generalized	6 (17%)	31 (23%)
Symptomatic generalized	5 (14%)	10 (8%)
Generalized and focal features	0	4 (3%)
Focal and PNES	0	2 (1%)

IQR = interquartile range; PNES = psychogenic nonepileptic seizures.

3.3.3. Subpopulation of patients with drug-resistant epilepsy (DRE) treated with MAD

Over 5 years, 112 participants met ILAE criteria for drug-resistant epilepsy, and 106 met all inclusion criteria for further subanalyses. Six did not meet inclusion criteria for further analyses: three were unable to take in oral nutrition as described in Section 3.3.2, two were not able to reliably quantify seizure frequency, and 1 was seen within 3 months of data analysis. The average number of antiseizure drugs tried was 7 (SD ± 3, median 6, range 2–18). Eighty-seven (82% of 106) elected to begin MAD, and 19 (18%) never started. Three participants (3%) provided initial feedback that they started MAD but subsequently did not follow up in clinic (i.e., 84 (79%) participants began MAD and were seen one or more times in follow-up; see Fig. 1). Thirty-three participants that began MAD and followed up at least once (39%) remained on the diet for the duration of the study, and 61% (n = 51) elected to stop. Efficacy and retention rates at 3 months, 6 months, and 1–5 years are included in Table 3 for those participants that have been followed for the specified duration or longer. Response rate (≥50% seizure reduction) was highest at 3 months at 36% (n = 38 of 106), with 16% (n = 17 of 106) of participants seizure-free from the time of diet initiation. In those participants followed for 4 or more years from the time of the initial visit, 21% responded (n = 6 of 29 followed 4 or more years), and 7% were seizure-free for 1 year or more (n = 2 of 29).

Forty-eight (57%) of 84 participants with DRE that began MAD had no antiseizure drug changes throughout the course of the treatment (Table 4). Of these, 17 (35% of 48) responded to MAD, and 7 (15%) were seizure-free at 3 months. One of the 11 (9%) participants that were seen at least 4 years prior to data analysis (first seen between August 2010 and October 2011) with DRE remained on MAD with no medication changes and was seizure-free. Ten of these participants stopped MAD.

Seven (8%) of 84 participants with DRE who began MAD were seizure-free (n = 4) or diet responders (n = 3) and elected to lower antiseizure drugs while remaining on MAD without a resultant increase in seizure frequency or severity. The remaining twenty-nine participants (35%) made changes to their antiseizure treatments (either increase in medication(s) or switch from one to another) during treatment.

3.3.4. Combined efficacy and adherence

Combined, 139 participants began (n = 133; 130 prescribed MAD, 1 prescribed KD, 2 prescribed combination diets) or continued (n = 35; 7 on KD, 2 transitioned from KD to MAD, 3 on combination diets, 1 transitioned from carbohydrate restriction to MAD) on a ketogenic diet after an initial clinic visit (Fig. 1). The combined diet duration ranged from 2 days to 36 years (mean 29 months (SD ± 57), median 9 months). Seventy-two (52%) remain on a ketogenic diet therapy as of data analysis. The average diet duration for these participants that have continued diet therapy is 45 months (range 2 months to 36 years, SD 70 months, median 28 months). Forty-one percent (57/139) have responded to diet therapy, and 27% (37/139) became seizure-free.

Of the remaining 67 (48% of 139) participants that are no longer on diet therapy, 52 (37%) elected to discontinue diet therapy (including 1 on KD, 1 on combination therapy, and 50 on MAD), 12 (9%) were lost to follow-up (all on MAD), 2 died (1%; 1 on KD and 1 on combination therapy), and 1 (1%) tapered off of MAD after being seizure-free for 1 year. Diet duration among patients that stopped diet therapy ranged from 2 days to 18 years (mean diet duration 10 months (SD ± 28), median 3 months).

Table 4
Treatment response and adherence in patients with drug-resistant epilepsy started on the Modified Atkins Diet with no increase in other antiseizure therapies during the study.

Clinic visit	Stopped	Worse or no change	<50% seizure reduction	≥50% seizure reduction	Seizure-free
3 months (n = 48)	21 (44%)	2 (4%)	8 (17%)	17 (35%)	7 (15%)
6 months (n = 47)	27 (57%)	1 (2%)	6 (13%)	13 (28%)	8 (17%)
1 year (n = 42)	29 (69%)	0 (0%)	2 (5%)	11 (26%)	7 (17%)
2 years (n = 33)	25 (76%)	0 (0%)	1 (3%)	7 (21%)	4 (12%)
3 years (n = 20)	16 (80%)	0 (0%)	0 (0%)	4 (20%)	2 (10%)
4 years (n = 11)	10 (91%)	0 (0%)	0 (0%)	1 (9%)	1 (9%)

3.4. Safety

One or more side effects were reported or identified in 54 (39%) of 139 participants during the course of the treatment with a ketogenic diet (Table 5). The most common side effects were weight loss (decrease in BMI ≥ 1 kg/m^2) which occurred in 19% of participants

Table 3
Treatment response and adherence in patients with drug-resistant epilepsy started on the Modified Atkins Diet.

Clinic visit	Never Started/No follow-up	Stopped	Worse or no change	<50% seizure reduction	≥50% seizure reduction	Seizure-free
3 months (n = 106)	22 (21%)	25 (23%)	6 (6%)	15 (14%)	38 (36%)	17 (16%)
6 months (n = 105)[a]	22 (21%)	38 (36%)	1 (1%)	12 (11%)	32 (31%)	15 (14%)
1 year (n = 98)[b]	21 (21%)	44 (45%)	0 (0%)	4 (4%)	29 (30%)	13 (13%)
2 years (n = 80)[c]	15 (19%)	45 (56%)	0 (0%)	4 (5%)	16 (20%)	6 (8%)
3 years (n = 56)[d]	13 (23%)	32 (57%)	0 (0%)	2 (4%)	9 (16%)	4 (7%)
4 years (n = 29)[e]	7 (24%)	16 (55%)	0 (0%)	0 (0%)	6 (21%)	2 (7%)
5 years (n = 3)[f]	0 (0%)	1 (33%)	0 (0%)	0 (0%)	2 (67%)	1 (33%)

[a] Duration of follow-up <6 months, n = 1.
[b] Duration of follow-up <1 year, n = 8.
[c] Duration of follow-up <2 years, n = 26.
[d] Duration of follow-up <3 years, n = 50.
[e] Duration of follow-up <4 years, n = 77.
[f] Duration of follow-up <5 years, n = 103.

Table 5
Side effects and adverse events in adults on ketogenic diets.

Side effect	n (% of 139 patients treated with ketogenic diet therapy unless otherwise specified)
LDL ≥ 130 mg/dL[a]	27 (29%, n = 92)
Weight loss	27 (19%)
Total cholesterol ≥ 240 mg/dL[a]	18 (20%, n = 92)
Triglycerides ≥ 150 mg/dL[a]	7 (8%, n = 92)
Worse seizures	8 (6%)
Constipation	5 (4%)
Weight gain	3 (2%)
HDL < 40 mg/dL	2 (2%, n = 92)
Acne	2 (1%)
Amenorrhea	2 (1%)
Carnitine deficiency	2 (1%)
Fatigue	2 (1%)
Nausea/Vomiting	2 (1%)
Newly diagnosed nephrolithiasis	2 (1%)
Newly diagnosed osteopenia/osteoporosis	2 (1%)
Abdominal pain	1 (<1%)
Alopecia	1 (<1%)
Cholecystitis	1 (<1%)
Diarrhea	1 (<1%)
Ecchymosis	1 (<1%)
Halitosis	1 (<1%)
Leg cramps	1 (<1%)
Serious adverse events	
Cardiac arrest	1 (<1%)
Sudden Unexplained Death in Epilepsy (SUDEP)	1 (<1%)

[a] When not elevated prior to ketogenic diet therapy and not corrected with continued treatment.

(n = 27) and hyperlipidemia (LDL ≥ 130 mg/dL, total cholesterol ≥ 240 mg/dL, and/or triglycerides ≥ 150 mg/dL at most recent lab collection and not seen prior to starting diet) in 36 (39%) of 92 participants in whom these laboratory results were available. The LDL became elevated in 27 (29% of 92), total cholesterol became elevated in 18 (20% of 92), and triglycerides became elevated in 7 (8% of 92). The HDL decreased below 40 mg/dL in 2 participants (2% of 92). More advanced lipid analyses have been presented in a prior publication in a subgroup of these participants [37]. Other common side effects included increased seizures (n = 8, 6%) and gastrointestinal complaints (n = 8 (6%); 5 with constipation, 2 with nausea and/or vomiting, 1 with abdominal pain). Weight loss was an intended or welcomed effect of the diet in 15 of 27 (56%) of the participants that lost weight on diet therapy. During the study period, 8 participants (6% of 139) received renal ultrasounds or abdominal CTs for symptoms concerning for nephrolithiasis, and 2 (25% of 8 that received a diagnostic study, 1% of 139 participants) were diagnosed with nephrolithiasis. Two participants (1%) had a history of nephrolithiasis prior to treatment without recurrence during the study. Eleven participants (8% of 139) received a bone density scan during the study period; 6 of whom had a history of osteopenia or osteoporosis prior to diet initiation. Two participants (1% of the 139 participants and 18% of the 11 that received bone density scans) were newly diagnosed with osteopenia or osteoporosis during the study period.

Regarding serious adverse events, one participant died of SUDEP 2 months after starting a MAD in combination with a ketogenic liquid supplement. The patient was a 39-year-old woman with a history of tuberous sclerosis complex, severe intellectual disability (nonverbal, wheelchair bound), and 4–10 focal seizures per month prior to diet initiation despite 4 antiseizure drugs and vagus nerve stimulation. A review of medical records indicates that she had not reached urine or serum ketosis at the time of death, and cause of death was deemed to be "seizure-related activity." Another participant experienced cardiac arrest after 18 years of treatment with the KD. This patient was a 22-year-old woman with mitochondrial complex I and III deficiencies with spastic quadriplegic cerebral palsy, intellectual disability (nonverbal), and status-post Nissen fundoplication with gastrostomy tube. These adverse events were deemed unlikely to be related to the ketogenic diet by the treating physicians. Formal autopsies were not performed.

3.5. Tapering ketogenic diets

Eighteen participants (13% of 139 participants on a ketogenic diet therapy) were seizure-free for 2 or more years while followed in the AEDC. Two (2%) were on a KD prior to the initial visit to AEDC and seizure-free on initial presentation, 6 (4%) were on MAD prior to the initial visit and seizure-free on presentation, and 10 (7%) were started on MAD de novo. When appropriate, these participants were asked if they wished to be tapered off of their ketogenic diet if follow-up electroencephalography showed no epileptiform activity, and all elected to remain on the diet with continued follow-up. One participant initially on KD for refractory status epilepticus transitioned to MAD once able to intake oral nutrition [36] and ultimately tapered off of MAD after 1 year of seizure freedom, without seizure recurrence.

When participants elected to stop MAD, a tapering schedule was recommended consisting of increasing carbohydrates by 5 g every 3 days until reaching 85 g per day and decreasing fat intake ad libitum, at which time the participant could resume their pre-MAD diet. Four (7%) participants that discontinued MAD (n = 57) noted an increase in seizures during the taper and elected to restart MAD, with return to their prior on-diet seizure frequency.

4. Discussion

To our knowledge, this represents the largest series to date prospectively examining the safety, tolerability, and efficacy of ketogenic diet therapies for adult epilepsy. This study also provides a detailed description of a structured Adult Epilepsy Diet Center (AEDC) and its development over 5 years. The majority of patients that attended the AEDC were women, and ages ranged widely from 18 to 86 years at the initial visit. Four-fifths of patients had never tried a ketogenic diet prior to the initial visit, and over half of patients traveled from out-of-state or internationally to attend clinic, suggesting that there is an unmet need for this treatment option for adults with epilepsy.

Overall, over half of participants who began a ketogenic diet remained on a diet throughout the study. Of all 139 participants that began or continued diet therapy after the initial visit, 41% (57 of 139) responded to diet therapy, and 27% (37 of 139) became seizure-free. Prior prospective studies have shown comparable results in smaller cohorts of adults at three and six months [18,20,22,24,27,28], but more long-term efficacy has not been previously studied in a large cohort.

For those specifically with DRE starting the MAD de novo, 16% (17 of 106) were seizure-free at 3 months, 13% (13 of 98) at 1 year, and 7% (2 of 29) at 4 years. A prior large study of patients with DRE reported a 4% rate of seizure freedom for 1 or more years after starting a 3rd drug or combination of drugs [38]. More recent antiseizure drug studies do not typically follow patients over several years. These findings suggest that head-to-head trials of ketogenic diets versus adjunctive antiseizure drug therapy may be justified in adults with DRE.

Approximately half of patients (48% or 67 of 139) discontinued the diet (n = 55, 39%) or were lost after initial follow-up (n = 12, 9%). Cited reasons for discontinuation included restrictiveness (51%), ineffectiveness (33%), side effects (9%), unrelated injury or death (5%), and diet tapering in the setting of seizure freedom without recurrence (2%). The majority (n = 51 of 55, 93%) discontinued within 6 months of establishing care. Among those beginning the MAD, the majority that stopped did so within the first 3 months of starting the diet. Reasons for stopping included difficulty with compliance (cited as the primary reason by nearly 50% of patients), insufficient seizure control, and side effects. Additional methods may improve compliance, including scheduled telephone calls or electronic communication with the supervising dietitian and use of Seizure Tracker®, KetoDietCalculator™, or

other electronic applications, particularly within the first 3 months of treatment to prevent early drop out [27].

Hyperlipidemia was the most common side effect, which has been reported in a subset of these patients and has been shown to reverse spontaneously in the majority of patients within the first year of treatment [37]. Weight loss was often an intended secondary effect and occurred in one-fifth of patients. Side effects were the reported reason for stopping the diet in less than 10% of patients while over half reported restrictiveness as the primary reason.

There were several important limitations to this study. Participants were typically highly motivated and self-referred and often had a secondary goal of weight loss, which may explain the larger proportion of female participants in the study. Participants that were eligible for participation in other clinical diet trials that are ongoing (those with 4 or more seizures per month on average, catamenial epilepsy on MAD, or a history of refractory status epilepticus treated with the ketogenic diet) were excluded, which may have biased the overall sample further. The study was uncontrolled and open-label, so the effects of changes in antiseizure drugs and other changes likely impacted overall efficacy over time. Two participants had known comorbid nonepileptic events that were clearly distinguishable from their epileptic seizures, but their seizure reporting could potentially be inaccurate. Finally, reported frequencies of detected side effects such as nephrolithiasis and osteopenia or osteoporosis are likely low because only a small fraction of participants received serial renal ultrasounds or bone density scans.

In conclusion, ketogenic diets may be safe and effective long-term treatments for adult epilepsy and are a promising adjunctive treatment for patients with drug-resistant epilepsy. The establishment of an Adult Epilepsy Diet Center has proved valuable to our epilepsy group and has helped improve an apparent unmet need. Despite overall seizure reduction and unlimited access to a registered dietitian and neurologist, diet adherence rates were still low long-term, and methods to improve compliance are necessary. Given that this was an observational study with a heterogeneous group of patients and that the results could have been due to placebo effect, further adequately controlled studies are necessary to determine the efficacy of ketogenic diets in the treatment of adults with epilepsy.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2016.02.038.

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