Epilepsy & Behavior 19 (2010) 575–579

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Ketogenic diet treatment in adults with refractory epilepsy

Pavel Klein [a,*], Jaromir Janousek [a], Arkady Barber [a], Randi Weissberger [b]

[a] Mid-Atlantic Epilepsy and Sleep Center, Bethesda, MD, USA
[b] Individualized Nutrition Counseling, Bethesda, MD, USA

ARTICLE INFO

Article history:
Received 8 July 2010
Revised 6 September 2010
Accepted 8 September 2010

Keywords:
Epilepsy
Seizures
Ketogenic diet
Lipids

ABSTRACT

The ketogenic diet (KD) is an effective treatment for refractory epilepsy in children. It has been little studied in adults. We evaluated the efficacy of, safety of, and compliance with adjunctive KD treatment in adults with refractory epilepsy in a prospective open-label pilot study. Seizure frequency was evaluated for 4 baseline months, 4 months of adjunctive KD treatment with a 3:1 [fat]:[carbohydrate + protein] weight ratio and 1600 kcal/day, and subsequent elective open-ended KD treatment. A 3:1 ratio was used instead of the 4:1 ratio employed in children because of greater palatability. Average monthly seizure frequency and seizure-free months at baseline were compared with KD months 1–4 (phase 1) and all KD treatment (phase 2). Diet compliance was evaluated with daily urine ketone body and monthly serum β-hydroxybutyrate levels. Twelve subjects were treated for up to 26 months. Three stopped treatment early for psychosocial reasons ($n = 2$) or lack of efficacy. Seven of the 12 subjects were fully compliant, 4 were partially compliant, and 1 was noncompliant. Mean seizure frequency declined by 38.4 and 44.1% for phases 1 and 2, respectively ($P = 0.04$). Forty-two percent and 50% of subjects had a >50% reduction during phases 1 and 2, respectively. Four of 12 subjects (33%) had a >85% seizure reduction. Twenty percent of subject-months were seizure free at baseline versus 56% during both study phases ($P = 0.04$). Adverse effects were mild: nausea, vomiting, diarrhea, constipation, and weight loss.

1. Introduction

Seizures in approximately 35% of patients with epilepsy fail to respond to antiepileptic drug (AED) treatment [1–3]. The ketogenic diet (KD) is a high-fat, low-protein, low-carbohydrate diet that is an effective treatment for refractory epilepsy in children [4,5]. The "classic" diet consists of long-chain saturated triglycerides with a 3:1 or 4:1 [fat]:[protein + carbohydrate] ratio by weight, with 90% of calories derived from fat. In open-label review or prospective studies of the KD in children, 7–15% of children with intractable epilepsy become seizure free, 25–40% have a 90% seizure reduction, and 55% have a >50% seizure reduction [6–11]. In a study of 145 children randomized to immediate KD versus KD delayed for 3 months, 38% of patients in the KD group achieved >50% and 7% >90% seizure frequency reduction versus 6 and 0% in the control group [9]. These results compare favorably with the efficacy of new AEDs, which lead to 1–7% seizure freedom rates and 90% seizure frequency reduction in fewer than 10% patients with intractable epilepsy [12,13].

Treatment with the KD is relatively safe. Potential side effects in children include constipation or diarrhea, nausea, vomiting, nephrolithiasis (3–7%), metabolic acidosis (2–5%), hyperuricemia (2–26%), hypocalcemia (2%), hypomagnesemia (5%), weight loss, hyperlipidemia, bruising, and osteopenia [4,5,14–17].

Despite its success in children, the KD has been little studied in adults. Only three studies in adults and one in adolescents have been published. In a 1930 study 100 adults were treated with KD monotherapy for 1 year, of whom 12% became seizure free, 44% improved and 44% remained unchanged [18]. More recently, there have been only two small reports. In one, 11 adults with refractory epilepsy were treated for 8 months with adjunctive 4:1 ratio KD. Three had >90%, three had 50–89%, and one had <50% seizure reduction; four stopped the diet prematurely [19]. Adverse events (AEs) included constipation and menstrual irregularities. In another study, nine adults with refractory epilepsy were to be treated with the KD for 12 weeks. Only two subjects completed the study, both with >50% seizure frequency reduction; the rest dropped out because of side effects (diarrhea, hunger, elevated lipids) and lack of efficacy [20].

Recently, two studies evaluated the "modified Atkins diet" in adults. This diet has a 0.9: 1 [fat]: [carbohydrate + protein] weight ratio, with 65% of calories derived from fat. In one study of 30 adults, 33% subjects achieved a >50% seizure reduction at 6 months; one subject became seizure free [21], and 33% stopped treatment before 3 months. In another study with carbohydrate restriction of 20 g/day, three of eight patients continued with the diet for 6 months, with seizure reductions of >50%, >30%, and <30% [22].

Given the apparent efficacy and safety of the KD in children and the lack of effective treatment in adults with intractable epilepsy, it is

* Corresponding author. Mid-Atlantic Epilepsy and Sleep Center, LLC 6410, Rockledge Drive, Suite 410, Bethesda, MD 20817, USA. Fax: +1 301 530 0046.
E-mail address: kleinp@epilepsydc.com (P. Klein).

1525-5050/$ – see front matter © 2010 Elsevier Inc. All rights reserved.
doi:10.1016/j.yebeh.2010.09.016

remarkable that the KD has not been evaluated more broadly in adults. The main reason appears to be an untested assumption that adults would not comply with the unpalatable diet. The goal of the present study was to obtain pilot data on compliance with and efficacy and safety of adjunctive KD treatment in adults with intractable epilepsy.

2. Methods

This prospective open-label study was approved by the institutional review board of Holy Cross Hospital, Silver Spring, MD, USA. Subjects signed institutional review board-approved consent forms. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

2.1. Subjects

Men and women aged 25–65 with refractory primary generalized (PGE) or localization-related (LRE) defined as failed treatment with three or more AEDs and seizure frequency of ≥1 every 2 months were recruited. Epilepsy was classified using ILAE criteria [23]. Exclusion criteria were renal, liver, cardiovascular or cerebrovascular (atherosclerotic), mitochondrial, or fatty acid metabolism disease, history of renal calculi, hyperuricemia, hypercalcemia, porphyria, and family history of hyperlipidemia.

2.2. Pretreatment evaluation

Subjects were evaluated by a team consisting of an epileptologist, a nutritionist, and a nurse. They met separately with each team member once or twice for 1-hour-long education visits. They were taught the caloric and compositional content of foods and how to determine it. Basal caloric intake was calculated from retrospective recall data and prospective (7 days) food records. A history of food allergies was obtained. Sample recipes and menus were created that incorporated the subject's food preferences. Subjects were given a set of these recipes and daily meal plans for five meals (three set meals and two snacks).

2.3. Initiation of the ketogenic diet

The ketogenic diet was initiated during a 4- to 5-day-long hospitalization. Subjects fasted for the first 24–48 hours, followed by daily caloric increase to 33, 66, and 100% of caloric target. Urine ketone levels were checked at each urination using Ketostix (Bayer AG, USA). Subjects were taught to do the measurements. Fast continued until urine ketones reached ≥40 mg/dL. Blood glucose was checked for possible hypoglycemia every 2 hours during the first 48 hours, then every 6 hours. The protocol included a glucose rescue plan if blood glucose fell to <50 mg/dL. The diet contained a 3:1 [fat]:[protein + carbohydrate] weight ratio with 1600 kcal/day caloric restriction, supplemented with vitamins, calcium, and phosphorus to meet the requirements of standard U.S. Dietary Reference Intakes. Caloric restriction was used based on traditional usage of the KD.

2.4. Maintenance of ketogenic diet

Subjects were seen by an epileptologist and a nutritionist 1 week, 3 weeks, 5 weeks, and 2 months after discharge, then monthly by the epileptologist and every 3 months by the nutritionist. If seizures did not improve after 2 months, the KD ratio was increased to 4:1.

2.5. Evaluations

Seizure frequency was evaluated prospectively for 4 months at baseline and 4–26 months after initiation of the KD with a daily seizure diary. AEDs were held stable during the baseline observation and KD period. At each visit, seizure frequency, treatment compliance, and AEs were evaluated and physical examination was performed. Body mass index (BMI) was calculated. Patients checked urine for ketones with Ketostix one to three times daily and documented results in a combined ketone/seizure diary which was reviewed at each visit. Urine Ketostix measures urine acetoacetate with a color-coded scale with ketone body (KB) level brackets of 15, 40, 80, and 160 mg/dL.

Diet compliance was assessed by measuring daily urine KBs and monthly serum β-hydroxybutyrate (BOHB) levels. Urine KB compliance was scored on a scale of 0–3, where 0 = no compliance (KB detectable on ≤75% of days); 1 = mild (KB = >15 <40 on ≥75% of days); 2 = moderate (KB ≥ 40 on ≥75% of days; 3 = complete (KB ≥ 40 on ≥95% of days). Undocumented days were counted as 0. Serum BOHB compliance was scored monthly as 1 when BOHB was elevated above normal (0–3 mmol/L), 0 when it was not, and calculated as the percentage of study months with compliance. Urine KB and serum BOHB compliances were converted to fractions (e.g., urine KB 1 = 0.33, 2 = 0.66, 3 = 1.00), combined, and averaged to yield an overall compliance score: <10% = 0, <50% = 1, <90% = 2, 100% = 3.

Quality of life was evaluated at each visit with the Patient-Weighted Quality of Life in Epilepsy inventory (QOLIE-31-P). Alertness was evaluated with the Epworth Sleepiness Scale (ESS).

Laboratory evaluations included CBC, CMP, BOHB, a.m. fasting (10-hour) lipid levels (cholesterol, triglycerides [TGs], high, low and very low density lipoprotein (HDL, LDL and VLDL), glucose and insulin levels, glycosylated hemoglobin (HBA_{1c}), leptin levels (because of the association of KD with weight loss and of serum leptin levels with weight loss), serum trough AED levels, and urine calcium and creatinine level (for risk of nephrolithiasis). These were done 1 month before KD initiation, on day 1 of the fast, and then monthly. Subjects treated for >3 months who stopped the diet had lipid levels checked monthly for 3 months after KD discontinuation.

The primary efficacy aim was comparison of average monthly seizure frequency during the 4-month baseline with that during the 4 months of KD treatment. Subjects who elected to continue KD treatment beyond 4 months were evaluated monthly for treatment months 5–12, then every 2 months. The secondary efficacy aim was comparison of average monthly seizures during baseline with those for the whole treatment duration.

Other outcome measures included proportion of seizure-free months, rate of KD discontinuation, AEs, weight, BMI, QOLIE-31-P scores, and ESS scores. Data were analyzed using Wilcoxon's test for nonparametric and Student's *t* test for normally distributed continuous variables (all two-tailed). Significance was set at $P<0.05$.

3. Results

3.1. Demographics/disease characteristics

Demographics, disease characteristics, and baseline treatment are summarized in Table 1. Twelve subjects were enrolled (eight women, four men, age range 24–65). An additional 23 eligible patients were screened and declined participation because of reluctance to give up their regular diet ($n=17$), the complexity of the KD ($n=5$), and cost. The screened to enrolled ratio was 35/12 (2.92).

3.2. Subject disposition

Treatment lasted 4 days to 26 months (Table 2). Three subjects discontinued treatment during the first 4 months for psychosocial reasons ($n=2$, at 4 days and 1.5 months) and lack of efficacy ($n=1$ at 2.5 months). Nine of twelve subjects elected to continue treatment past the initial 4-month study period, including six subjects treated for

Table 1
Patient demographics and epilepsy/seizure and clinical characteristics.

Subject No.	Sex	Age	Epilepsy type	Age at epilepsy onset	Seizure type	No. of past AEDs	Current AEDs (mg/day)	Comorbidity
1	F	24	PGE[a]	7	GTC, Abs, Myo	8	TPM 1000 VNS (inactive)	Obesity, depression, $\downarrow T_4$
2	F	40	PGE	3	GTC, Abs, Myo	7	TPM 350	Obesity, OSA, hypertension, peptic ulcerative disease, $\downarrow T_4$
3	M	34	PGE	23	GTC	3	LEV 3000, TPM 50	Obesity, OSA
4	F	46	PGE/JME	10	GTC, Abs, Myo	8	LEV 5000, LTG 600	Obesity, OSA, depression
5	F	65	PGE	27	GTC, Myo	2	LEV 2000	Obesity, OSA, depression, non-insulin-dependent diabetes mellitus
6	F	44	LRE	10	CPS	7	LEV 3000, TPM 400, LTG 300, CBZ 600	Obesity, OSA, perimenopause
7	F	53	LRE	2	CPS	8	TPM 200, OXC 2100	Obesity, perimenopause
8	F	33	LRE	13	CPS	8	OXC 1800, LTG 425, TGB 10	None
9	M	37	LRE	31	SPS/CPS	6	LEV 4500, PGB 800, VPA 2000, CBZ 1200	Neurocytoma, obesity,
10	F	40	LRE	12	CPS	5	LEV 3000, CBZ 1400, VNS	Obesity
11	M	35	LRE	25	SPS/CPS	6	LEV 3000, OXC 600, PGB 800	Anxiety
12	M	24	LRE	10	CPS/GTC	2	OXC 600	Autism, pervasive developmental disorder

[a] PGE, primary generalized epilepsy; LRE, localization-related epilepsy; Ab, absence seizures; Myo, myoclonic seizures; GTC, generalized tonic–clonic; CPS, complex partial seizures; SPS, simple partial seizures; CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; OXC, oxcarbazepine; PGB, pregabalin; TGB, tiagabine; TPM, topiramate; VPA, valproate; $\downarrow T_4$, hypothyroidism; OSA, obstructive sleep apnea; VNS, vagus nerve stimulation.

>8 months and four subjects treated for ≥20 months. Four subjects stopped the KD after 7, 8, 24, and 25 months because of an unplanned pregnancy ($n=1$) and a desire for regular food ($n=3$). Five subjects are still in treatment (duration: 6–20 months).

3.3. Treatment compliance

Seven of twelve subjects were fully compliant (three on the scale of 0–3), including the subject who stopped the KD for lack of efficacy. Two of twelve subjects were moderately (2) and mildly (1) compliant. One subject was noncompliant (0) and stopped treatment after 4 days (Table 2).

3.4. Seizure control

Tables 2 and 3 summarize data on generalized tonic–clonic seizures (GTC) in subjects with PGE and complex partial seizures (CPS) in subjects with LRE. Because of the lesser reliability of absence, myoclonic, and simple partial seizure counts, data analysis below is confined to GTC seizures/CPS. Data on absence, myoclonic, and simple partial motor seizures are summarized in Supplemental Table 2a (see Appendix A).

Ten of twelve subjects improved, one did not change, and one worsened. Average monthly seizure frequency for the 11 subjects treated for >1 week declined by 38.4% for KD months 1–4 ($P=0.05$) and by 44.1% for the whole treatment duration ($P=0.04$). Four of twelve (33%) subjects had a >75% seizure reduction, including one subject who stopped treatment after 1.5 months; excluding her, 3 of 12 (25%) subjects did. Five of twelve (42%) subjects had a >50% seizure reduction during KD months 1–4, and 6 of 12 (50%) during the whole treatment; an additional 4 of 12 subjects experienced 20–50% seizure reductions during both study phases. During baseline, 20% of subject-months were seizure-free compared with 56% during both study phases ($P=0.04$).

Response to treatment was fast. In all subjects with a >75% seizure reduction, the full effect occurred during the first month of treatment. In four subjects with daily absence/myoclonic seizures, response reached its full extent within 4 days of KD initiation.

Three subjects with a >75% seizure reduction (two with PGE, one with LRE) stopped the diet, after 1.5, 8, and 18 months. In all three, seizures returned to pretreatment frequency after 1–7 months. One successfully restarted the KD.

Two subjects with no improvement on the 3:1 diet (both fully compliant) increased the [fat]:[carbohydrate/protein] ratio to 4:1

Table 2
Monthly frequency of only generalized tonic–clonic and complex partial seizures for 4-month baseline, KD treatment months 1–4, and whole treatment duration.

Subject No.	Treatment duration (months)	Seizure frequency/month			% Change		AED change on KD	Compliance[a]
		Baseline	KD months 1–4	Whole treatment	KD months 1–4	Whole treatment		
1	7	2	0.5	0.29	75	85.5	0	3
2	26	0.75	0.5	0.48	33	36	0	1
3	20	0.75	0.5	0.26	33.3	65.3	dc 2/2	2
4	1.5	1	0	0	100	100	0	2
5	6	0.5	0	0.17	100	66	0	3
6	25	0.75	0.75	0.44	0	41.4	0	1
7	20	8	1	0.97	87.5	87.9	0	3
8	2.5	2.25	5.6	5.6	−149	−149	0	3
9	9	0.75	0.5	0.46	33	38.7	dc 1/4, ↓dose 2/4	3
10	7	5	0.75	0.6	85	88	0	3
11	16	1	0.75	0.75	25	25	0	3
12[b]	0.13	na	na	na	na	na	na	0
Mean (SD)		2.07 (2.36)	0.99[c] (1.56)	0.91[d] (1.58)	38.44	40.58		

[a] Compliance grading: 0 = none; 1 = mild, 2 = moderate, 3 = complete.
[b] Subject dropped out after 4 days and is not included in data analysis.
[c] $P=0.05$.
[d] $P=0.04$.

Table 3
Seizure-free months for 4-month baseline, KD months 1–4, and whole treatment duration.

Subject No.	Treatment duration (months)	Seizure-free months			Compliance[b]
		Baseline	KD months 1–4[a]	Whole treatment	
1	7	0	2	4/7	3
2	26	2	4	16/26	1
3	20	2	1	17/19	2
4	1.5	0	1.5/1.5	1.5/1.5	2
5	6	3	3	4/6	3
6	25	2	4	16/22	1
7	20	0	2	8/18	3
8	2.5	0	0/2.5	0/2.5	3
9	9	0	2	4/9	3
10	7	0	3	6/7	3
11	16	0	0	2/16	3
12[c]	0.13	N/A	N/A	Na	0
Total		9/44	22.5/40	78.5/140	
% seizure free		20	56.2[d]	56.1[d]	

N/A, not applicable.
[a] Treatment months 1–4 are 4 months except for subjects who discontinued treatment early, for whom number of seizure-free months/number of months on treatment is given.
[b] Compliance grading: 0 = none; 1 = mild, 2 = moderate, 3 = complete.
[c] Subject dropped out after 4 days and is not included in data analysis.
[d] $P = 0.04$.

Table 4
Effect of KD on BMI, weight, and blood leptin levels.

Subject No.	BMI (kg/m^2)[a]			Weight (lb)[a]		Leptin (ng/mL)[a]	
	Baseline	KD	% Change	Baseline	KD	Baseline	KD
1	34.2	25.8	24.6	193	146	na	na
2	44.2	32.3	26.9	274	194	31.4	12.6
3	34	30.5	10.3	230	195	35.4	7
4	44.1	41.6	5.7	265	250	66.9	61
5	28.9	24	17	179	149	20.2	9.4
6	33.3	28.7	15.8	194	167	22.4	14.8
7	38.3	24.6	35.8	230	148	21.9	4.4
8	22.1	21.6	2.3	140	136	7.7	2.1
9	33.4	23.4	30	260	182	27.8	5.7
10	34.2	28.3	17.3	199	165	27.7	10.1
11	25.4	21.5	15.4	177	150	4.1	1.9
Mean	33.83	27.48[b]	18.3	212.82	171.05[b]	26.55	12.9[c]
(SD)	(6.83)	(5.87)		(42.37)	(32.9)	(17.23)	(17.43)

[a] Lowest BMI/weight/leptin level during treatment. BMI and leptin levels are rounded to the nearest decimal point, weight to the nearest pound.
[b] $P<0.001$.
[c] $p<0.001$.

after 2 months. One did not improve and stopped the diet. Another subject improved and has continued with the diet (17 months to date).

Antiepileptic drugs were held constant in 9 of 11 subjects treated for >1 week. Two subjects reduced AEDs: one subject decreased from four to three AEDs at 6 months, and another subject self-discontinued two of two AEDs after 1 month and has continued on the KD alone (20 months to date).

3.5. Safety and tolerability

No subjects discontinued treatment because of AEs. AEs were mild and included transient nausea ($n = 1$), diarrhea ($n = 2$), and constipation ($n = 1$) during KD initiation, and nausea (n = 2), isolated vomiting ($n = 2$), abdominal cramps ($n = 1$), and mild intermittent constipation (n = 4) during KD maintenance. Three subjects (25%) had mild intermittent hunger, rated 2–3 on a scale of 10.

3.6. Weight

Caloric intake was reduced from a baseline average of 2412 kcal/person/day (range = 2100–2750, median = 2400) to 1600 kcal/day. All 11 subjects treated for >1 week lost weight (Table 4). Their mean weight declined by 38.7 lb from 212.8 lb at baseline to 171.1 (range = 4–80 lb, $P<0.001$). Mean BMI was reduced by 18.3%, from 33.8 to 27.5 kg/m^2 (range = 2.3–35.8%, $P<0.001$). Eight of nine overweight or obese subjects (BMI = 25–29.9 and ≥30 kg/m^2, respectively [24]) had a ≥10% BMI reduction, seven of nine ≥15%, and four of nine ≥20%. The only obese subject who lost <10% of BMI stopped treatment after 1.5 months. One overweight and two obese subjects normalized their BMI, and a third obese patient near-normalized it (BMI = 25.8). The weight loss was associated with reduction of mean serum leptin levels in 10 of 10 subjects in whom leptin was measured, from mean baseline 26.6 ng/mL to 12.9 ng/dL ($P = 0.001$).

3.7. Lipids, glucose, and other labs

Mean serum cholesterol levels increased from 213.7 to 257.8 mg/dL ($P = 0.04$). TG, HDL, LDL, and VLDL levels did not change significantly (Table 5). Five of six subjects who stopped the KD after >1 month had an increase in serum lipids on the KD. Lipid levels returned to baseline within 3 months of stopping KD, including 3 subjects treated with statins, in whom statins were stopped after the KD was discontinued. Mean fasting glucose levels were higher at baseline compared with KD maintenance (87.7 mg/dL vs 78.7 mg/dL, $P = 0.04$). Mean glucose levels declined during KD initiation, from 82.26 mg/dL on days 1–2 to 69.27 mg/dL on days 3–5 ($p = 0.008$). There was no significant change in mean peak plasma uric acid levels: 5.6 mg/dL at baseline versus 6.06 mg/dL on the KD.

3.8. Quality of life

Mean QOLIE-31-P global scores rose nonsignificantly from 5.25 at baseline to 7. ESS scores did not change significantly (7.9/24 at baseline vs 7.4/24 at last KD visit).

4. Discussion

This open-label study of adjunctive KD treatment in adults with refractory epilepsy resulted in overall seizure improvement, including >75% seizure frequency reduction in 25% of subjects treated for >4 months. The treatment was well tolerated and had good compliance. The study shows that KD treatment in adults is feasible. The study differs from the two previous completed studies of KD treatment in adults with epilepsy in that the treatment duration was long and there was follow-up of subjects after treatment discontinuation to evaluate possible disease-modifying properties of the KD in adults. It is the first study of KD treatment, to our knowledge, to incorporate quantitative measurement of compliance. Limitations of the study include its small size, uncontrolled selection of subjects, and the open-label, nonrandomized design.

Despite its success in the treatment of children with refractory epilepsy, the KD has been little evaluated in adults with refractory epilepsy, with only 20 subjects in two studies reported since 1930, and only 13 of these subjects treated for 12 weeks or longer [19,20]. The assumption has been that adults may not comply with the unpalatable and complicated diet. The present study suggests that this may not be true. The “modified Atkins” diet has been tried in adults instead of the KD in the belief that compliance would be better [21,22]. The Atkins diet shares with the KD carbohydrate restriction. However, it differs significantly from the classic ketogenic diet: only 60–65% of calories are fat-derived, and protein content is higher. It has been less studied in children than the KD. We therefore chose to study the "classic" KD.

Table 5
Fasting serum lipid levels at baseline and on KD, measured at the end of KD treatment (the last value for subjects still on treatment) or before initiation of treatment with lipid-lowering agents (statins, $n=3$).

Subject No.	Baseline					KD					Statin treament
	Chol	TG	HDL	VLDL	LDL	Chol	TG	HDL	VLDL	LDL	
1	220	68	62	14	145	241	121	49	24	168	Yes
2	164	42	50	8	106	159	36	75	7	77	
3	280	195	39	39	202	238	78	45	16	177	
4	214	62	63	12	139	214	69	79	14	121	
5	181	154	53	30.8	99.7	201	131	62	25	117	
6	181	73	63	14.6	54.4	210	76	80	15	109	
7	193	114	50	22.8	96.8	398	184	46	37	315	Yes
8	245	56	87	11	162	385	111	65	22	298	Yes
9	261	311	37	62	162	312	427	33	66	na	
10	237	50	105	10	122	284	73	75	15	194	
11	175	95	47	19	105	186	82	62	16	108	
Mean	213.7	110.9	59.6	22.1	139.9	257.8[a]	125.9	60.4	25.5	168.4	
(SD)	(38.38)	(81.47)	(20.4)	(16.3)	(40.52)		(107.3)	(15.82)	(16,16)	(81.27)	

[a] $P=0.04$.

We used the 3:1 ratio because it may be more palatable than the 4:1 ratio often used in children. Seventy-five percent of our subjects completed the planned 4 months of the study and elected to continue KD treatment beyond the initial 4 months. This rate of subject retention is similar to retention rates in investigational AED phase 3 studies and their open-label extensions [12]. However, two thirds of potentially eligible subjects declined to participate because of the restrictive and complex nature of the diet. This made recruitment into the study challenging, and could be a limiting factor in larger KD studies.

The efficacy data in this study are similar to those from pediatric studies, and suggest that the KD may be very effective in a proportion of adults. Twenty-five percent of our subjects treated long term had a >75% seizure frequency reduction and 42% had a >50% reduction. This is in line with a recent randomized pediatric study in which 38% of subjects had a >50% and 7% had a >90% seizure frequency reduction [9], and is similar to the only other completed "modern" adult KD study in which 3 of 11 subjects had a >90% seizure reduction and 55% had a ≥50% seizure decrease [20]. That study diet used a 4:1 [fat]: [carbohydrate/protein] ratio. Our data suggest that the 3:1 ratio may be similarly effective.

In pediatric studies, the antiepileptic effect may persist after KD discontinuation [11]. Adult studies have not previously evaluated the effect of KD on epilepsy after treatment discontinuation. In our study, seizure improvement did not outlast KD treatment. This indicates a possible difference between adult and pediatric responses to the KD.

Treatment noncompliance is a common trigger of seizures [25]. It can be expected to be worse with the KD because of the diet's restrictive and complicated nature, making monitoring important. We used combined quantitative self-reported daily urine and serum ketone body level measurements, allowing comparison of subject-based and subject-independent compliance evaluation that could be used in future studies. Monitoring diet compliance with urinary ketosis has limitations because urinary ketosis may be reduced by factors other than compliance, such as use of carbohydrate-containing medications, liver dysfunction, or overhydration; however, at present, it is the only method available short of direct food intake observance.

Appendix A. Supplemental data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.yebeh.2010.09.016.

References

[1] Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med 2000;342:314–9.
[2] Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic–clonic seizures. N Engl J Med 1985;313:145–51.
[3] Cascino GD. When drugs and surgery don't work. Epilepsia 2008;49(Suppl 9):79–84.
[4] Hartman AL, Vining EP. Clinical aspects of the ketogenic diet. Epilepsia 2007;48:31–42.
[5] Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia 2009;50:304–17.
[6] Freeman JM, Vining EPG, Pillas DJ, Casey JC, Kelly LM. The efficacy of the ketogenic diet—1998: a prospective evaluation of intervention in 150 children. Pediatrics 1998;102:1358–63.
[7] Lefevre F, Aronson N. Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy. Pediatrics 2000;105(E46):1–7.
[8] Keene DL. A systematic review of the use of the ketogenic diet in childhood epilepsy. Pediatr Neurol 2006;35:1–5.
[9] Neal EG, Chaffe HM, Edwards N, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol 2008;7:500–6.
[10] Hartman AL, Gasior M, Vining EPG, Rogawski MA. The neuropharmacology of the ketogenic diet. Pediatr Neurol 2007;36:281–92.
[11] Hemingway C, Freeman JM, Pillas DJ, Pyzik PL. The ketogenic diet: a 3- to 6-year follow-up of 150 children enrolled prospectively. Pediatrics 2001;108:898–905.
[12] Gazzola DM, Balcer LJ, French JA. Seizure-free outcome in randomized add-on trials of the new antiepileptic drugs. Epilepsia 2007;48:1303–7.
[13] Kwan P, Brodie MJ. Emerging drugs for epilepsy. Expert Opin Emerg Drugs 2007;12:407–22.
[14] Vining EP. Long-term health consequences of epilepsy diet treatments. Epilepsia 2008;49(Suppl 8):27–9.
[15] Kang HC, Chung da E, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia 2004;45:1116–23.
[16] Furth SL, Casey JC, Pyzik PL, et al. Risk factors for urolithiasis in children on the ketogenic diet. Pediatr Nephrol 2000;15:125–8.
[17] Kwiterovich Jr PO, Vining EP, Pyzik P, Skolasky R, Freeman JM. Effect of a high-fat ketogenic diet on plasma levels of lipids, lipoproteins, and apolipoproteins in children. JAMA 2003;290:912–20.
[18] Barborka C. Epilepsy in adults: results of treatment by ketogenic diet in one hundred cases. Arch Neurol 1930;6:904–14.
[19] Sirven J, Whedon B, Caplan D, Liporace J, Glosser D, O'Dwyer J, et al. The ketogenic diet for intractable epilepsy in adults: preliminary results. Epilepsia 1999;40:1721–6.
[20] Mosek A, Natour H, Neufeld MY, Shiff Y, Vaisman N. Ketogenic diet treatment in adults with refractory epilepsy: a prospective pilot study. Seizure 2009;18:30–3.
[21] Kossoff EH, Rowley H, Sinha SR, Vining EPG. A prospective study of the modified Atkins diet for intractable epilepsy in adults. Epilepsia 2008;49:316–9.
[22] Carrette E, Vonck K, de Herdt V, et al. A pilot trial with modified Atkins' diet in adult patients with refractory epilepsy. Clin Neurol Neurosurg 2008;110:797–803.
[23] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989;30:389–99.
[24] Aronne LJ. Classification of obesity and assessment of obesity-related health risks. Obes Res 2002;10:105S–15S.
[25] Mattson RH. Emotional effects on seizure occurrence. Adv Neurol 1991;55:453–60.