Dietary treatment in adults with refractory epilepsy

A review

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ABSTRACT

We review adjunctive ketogenic diet (KD) and modified Atkins diet (MAD) treatment of refractory epilepsy in adults. Only a few studies have been published, all open-label. Because of the disparate, uncontrolled nature of the studies, we analyzed all studies individually, without a meta-analysis. Across all studies, 32% of KD-treated and 29% of MAD-treated patients achieved ≥50% seizure reduction, including 9% and 5%, respectively, of patients with >90% seizure frequency reduction. The effect persists long term, but, unlike in children, may not outlast treatment. The 3:1 and 4:1 [fat]:[carbohydrate + protein] ratio KD variants and MAD are similarly effective. The anticonvulsant effect occurs quickly with both diets, within days to weeks. Side effects of both diets are benign and similar. The most serious, hyperlipidemia, reverses with treatment discontinuation. The most common, weight loss, may be advantageous in patients with obesity. Potential barriers to large-scale use of both diets in adults include low rate of diet acceptance and high rates of diet discontinuation. The eligible screened/enrolled subject ratios ranged from 2.9 to 7.2. Fifty-one percent of KD-treated and 42% of MAD-treated patients stopped the diet before study completion. Refusal to participate was due to diet restrictiveness and complexity, which may be greater for KD than MAD. However, long-term adherence is low for both diets. Most patients eventually stop the diet because of culinary and social restrictions. For treatment of refractory status epilepticus, only 14 adult cases of KD treatment have been published, providing insufficient data to allow evaluation. In summary, KD and MAD treatment show modest efficacy, although in some patients the effect is remarkable. The diets are well-tolerated, but often discontinued because of their restrictiveness. In patients willing to try dietary treatment, the effect is seen quickly, giving patients the option whether to continue the treatment. *Neurology*® 2014;83:1978–1985

GLOSSARY

AED = antiepileptic drug; **BHB** = β-hydroxy-butyrate; **BMI** = body mass index; **FDA** = US Food and Drug Administration; **KD** = ketogenic diet; **LRE** = localization-related epilepsy; **MAD** = modified Atkins diet; **PGE** = primary generalized epilepsy; **RSE** = refractory status epilepticus.

Approximately 60%–65% of patients with epilepsy become seizure-free with antiepileptic drug (AED) treatment.[1] The remaining 35% are resistant to medications. Between 1993 and 2013, 16 new chronic-use AEDs were approved by the US Food and Drug Administration (FDA), including 5 with novel mechanisms of action. This has not resulted in a significant decrease in refractory epilepsy. There is therefore a need for new treatment of refractory epilepsy. Ketogenic diet (KD) is a promising alternative therapeutic option.

In the last decade, there has been exponential growth in interest in the use of KD in treatment of epilepsy. Initially, this concentrated on children. In the last few years, the interest has spread to adults, with adult ketogenic and modified Atkins diet programs springing up in epilepsy centers all across the United States and Europe. However, the use of KD in adults is based largely on pediatric experience. Our goal is to review the adult data.

The paucity of studies of KD and modified Atkins diet (MAD) in adults with epilepsy (tables 1 and 2) challenges a traditional review approach. We therefore describe in some detail one study each of KD and MAD to highlight the opportunities and challenges of using KD and MAD in

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Table 1 Summary of efficacy data of 5 studies of adjunctive ketogenic diet treatments in adults with refractory epilepsy[21–25]

Reference	Subjects, n	KD	Study duration, mo	Rx dropout	Rx completion	>90% sz ↓	≥75% sz ↓	≥50% sz ↓	<50% sz ↓	sz ↑
Sirven et al.[21]	11	4:1	8	4	7	3	4	6	1	0
Nei et al.[22]	29[a]	4:1	6/24	18/24	11/5	NA	6	13	4	3
Mosek et al.[23]	9	4:1	3	7	2	0	0	2	0	2
Klein et al.[24]	12	3:1	4–26	3	9	1	4	5	5	1
Lambrechts et al.[25]	15	3:1 or MCT	12	10	5	0	NA	2	3	5
Total, n (%)	47			24 (51)	23 (49)	4 (9)	8 (17)	15 (32)	9 (19)	8 (17)

Abbreviations: KD = ketogenic diet; MCT = medium chain triglycerides; NA = not available; sz = seizures.
[a] Includes 11 adult subjects of the Sirven et al. report, 1 child aged 11 years, and subjects aged 17 years and older. Because of this, patients from this report are not included in the total numbers in the table.

adults. We did not do a meta-analysis of the studies because of the lack of randomized controlled aspects of any of the studies and the small number of studies and subjects.

All studies reviewed here provide Class III evidence. There are additional case reports in the literature, which we do not include. No Class I–II studies exist in adults. In children, only 2 Class II studies exist, one each for KD[2] and MAD[3]; the rest are also Class III–IV.

KETOGENIC DIET KD is a high-fat, low-carbohydrate diet.[4,5] The classic diet consists of long chain saturated triglycerides with a 3:1 or 4:1 [fat]:[carbohydrate + protein] ratio by weight, with 87%–90% of calories derived from fat. By contrast, the typical American diet derives about 50% of calories from carbohydrate, 35% from fat, and 15% from protein. US governmental guidelines for adults recommend 45%–65% calories from carbohydrates, 10%–20% from fat, and 10%–35% from protein.

In children with intractable epilepsy treated adjunctively with KD in uncontrolled open-label prospective studies, 7%–15% become seizure-free, 25%–40% have 90% seizure reduction, and 55% have ≥50% seizure reduction.[2,6–10] In a controlled study of 145 children randomized to immediate KD vs KD delayed for 3 months, 38% of patients in the KD group achieved >50% and 7% >90% seizure frequency reduction vs 6% and 0% in the control group.[2] These results compare favorably with efficacy of new AEDs, which have seizure freedom rate of 1%–7%, and 90% seizure frequency reduction in ≤10% patients with intractable epilepsy.[11] KD treatment in children has a favorable side effects profile.[4,5,12–14] Potential side effects 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.[4,5,12–14] Isolated cases of pancreatitis have been reported, but only in patients on valproate, a well-known cause of pancreatitis.

The mechanism by which KD prevents seizures remains poorly understood. Four main mechanisms have been proposed: (1) increased GABA synthesis; (2) increased adenosine-mediated neuronal inhibition; (3) increased activity of ATP-sensitive potassium channels leading to membrane hyperpolarization; and (4) reduced uptake of glutamate by synaptic vesicles resulting in reduced synaptic glutamate release.[15] Patients and animals treated with KD have increased blood levels of ketone bodies and decreased

Table 2 Summary of efficacy data of 5 studies of adjunctive modified Atkins diet treatment in adults with refractory epilepsy[28–32]

Reference	Subjects, n	Study duration, mo	Rx dropout	Rx completion	>90% sz ↓	≥75% sz ↓	≥50% sz ↓	<50% sz ↓	sz ↑
Carrette et al.[29]	8	6	5	3	0	0	1	2	0
Kossoff et al. (2008)[28]	30	6	16	14	1	4	10	5	0
Smith et al.[30]	18	12	4	14	0	1	3	4	7
Cervenka et al.[31]	22[a]	3	8	14	3	NA	6	NA	NA
Kossoff et al. (2013)[32]	7[b]	3	3	5	3	3	4	0	0
Total, n (%)	85		36 (42)	50 (59)	7 (8)	NA	24 (28)	NA	NA

Abbreviation: NA = not available; sz = seizures.
[a] A total of 25 patients consented to participate; 22 started the diet. E-mail follow-up only.
[b] Patients with juvenile myoclonic epilepsy only.

levels of glucose. Substitution of glucose by ketones for energy supply results in decreased glycolysis and increased Krebs cycle activity. This results in increased production of GABA, although increased GABAergic neurotransmission has not been observed. It also appears to increase extracellular adenosine levels (from ATP breakdown), inhibiting excitability through activation of the adenosine A1 receptor.[16] In addition, KD results in activation of ATP-sensitive potassium (KATP) channels, probably by reducing their inhibition by intracellular ATP, resulting in neuronal hyperpolarization.[17] Finally, aceto-acetate blocks glutamate packaging into excitatory synaptic vesicles, thereby reducing glutamate release.[18]

In spite of its success in children, KD has been little studied in adults. The main reason appears to be an untested assumption that adults may not comply with the unpalatable diet. Only 6 studies in adults have been published.

In the 1920s and 1930s, before the advent of phenytoin in 1938, KD was the mainstay of epilepsy treatment.[19] In a 1930 study of 100 adults treated with KD monotherapy for 1 year, 12% became seizure-free, 44% improved, and 44% remained unchanged.[20] Since the resurgence of KD in the 1970s, there have only been 5 reports of KD treatment in adults with epilepsy. All were prospective, open-label, uncontrolled studies of adjunctive KD treatment in treatment-resistant epilepsy. The efficacy and retention data from these studies are summarized in table 1.

In the first study, 11 adults were treated for 8 months with adjunctive 4:1 ratio KD without caloric restriction.[21] Four patients stopped the diet prematurely because of lack of efficacy (n = 2) and poor compliance; none due to side effects. In 7/11 (64%) patients, seizure frequency improved. One patient (9%) became seizure-free, 27% had >90% seizure frequency reduction, 36% had >75%, and 55% had >50% seizure reduction. Mean seizure frequency reduction was 43% for localization-related epilepsy (LRE) and 51% for primary generalized epilepsy (PGE) (table 3), but the sample was too small for meaningful efficacy comparison between different epilepsy types. Side effects included constipation and bloating in all patients, menstrual irregularities (all women), hunger in 73%, weight loss in 45%, and impaired concentration in 18%. Sixty-four percent of subjects had improved cognition. Mean serum cholesterol increased by 40% from 208 to 291 mg/dL. Triglyceride level rose by 7% from 190 mg/dL at baseline to 203 mg/dL (table 3).

This study was continued long term and its extension has just been published.[22] The extended study treated 29 patients (including the original 11), including 1 child aged 11 and 28 patients aged ≥17 years. Treatment duration goal was 24 months. Only 38% (11/29) of patients continued the diet for 6 months, and 17% for ≥23 months. Reasons for diet discontinuation included difficulty with compliance (n = 11) and lack of efficacy (n = 9). Thirteen

Table 3 Effects of adjunctive ketogenic diet[18-21] and modified Atkins diet[24-28] treatment on seizures by epilepsy type (localization-related vs primary generalized epilepsy) and on lipids in adults with refractory epilepsy

Reference	Subjects, n (LRE/PGE)	Diet	LRE % sz ↓	PGE % sz ↓	% Cholesterol ↑	% TG ↑
Sirven et al.[21]	11 (6/5)	4:1	43	51	40	7
Nei et al.[22]	29[a]	4:1	NA	NA	21	26
Mosek et al.[23]	9 (NA)	4:1	NA	NA	33	0
Klein et al.[24]	12 (7/5)	3:1	30	68	21	14
Lambrechts et al.[25]	15 (11/NA)	3:1 or MCT	NA	NA	NA[b]	NA
Total KD	47		37	60	31	11
Carrette et al.[29]	8	MAD	NA	NA	NA	NA
Kossoff et al. (2008)[28]	30 (23/?)	MAD	NA	NA	7	−18
Smith et al.[30]	18	MAD	NA	NA	NA	−36
Cervenka et al.[31]	22 (NA)	MAD	NA	NA	34[c]	24
Kossoff et al. (2013)[32]	7 (0/7)[d]	MAD	NA	56	NA	NA
Total MAD	85		NA	56	21	−10

Abbreviations: KD = ketogenic diet; LRE = localization-related epilepsy; MAD = modified Atkins diet; MCT = medium chain triglycerides; NA = not available; PGE = primary generalized epilepsy; sz = seizures; TG = triglycerides.
Percentages are rounded to the nearest whole number.
[a] Includes 11 adult subjects of the Sirven et al. report, 1 child aged 11 years, and subjects aged 17 years and older. Because of this, patients from this report are not included in the total numbers in the table.
[b] Two patients developed lipid disorders; no other information available.
[c] Lipid values were available for only 9 patients.
[d] All patients had juvenile myoclonic epilepsy.

patients (45%) had ≥50% seizure frequency reduction, including 21% patients with ≥80% seizure frequency reduction. Thirty-one percent of patients had no improvement and 10% had >50% seizure increase. Of note, one patient was seizure-free for 1 year, but then stopped the diet because of difficulty with compliance. Fourteen patients had symptomatic generalized epilepsy, 11 focal and 4 PGEs. There was a trend for patients with symptomatic generalized epilepsy to have greater seizure frequency reduction: 64% of those patients had ≥50% seizure reduction and 36% had ≥80% reduction vs 28% and 7%, respectively, in patients with focal epilepsy (p = 0.11). Three of the 4 PGE patients had seizure improvement, including 2/4 with >50% seizure frequency reduction, including one with seizure freedom (personal communication, Dr. Nei, 2014), and one with unquantifiable seizure reduction, from multiple daily absence seizures to 1 hour-long period of repetitive absence seizures per week.

The most common side effects were constipation (n = 5) and weight loss (most patients). Mean weight loss was −7.98 kg. Mean cholesterol level increased by 21% from 216 mg/dL at baseline to 261 mg/dL at diet termination. Three patients continued with MAD after completing 24 months of KD. Seizures continued to be improved in 2, but with improvement rate declining from 80% to 50%, and reverted back to baseline in 1.

In another study, 9 adults with refractory epilepsy were to be treated with 4:1 KD without caloric restriction for 12 weeks.[23] Only 2 subjects completed the study, both with >50% seizure frequency reduction. Seven of 9 subjects dropped out because of side effects (diarrhea n = 1, hunger n = 1, hyperlipidemia n = 1) and lack of efficacy (n = 3). Mean cholesterol levels increased from 199 mg/dL at baseline to 266 mg/dL at 11–12 weeks of KD treatment, low-density lipoprotein levels from 115 mg/dL to 177 mg; both declined to baseline 5 weeks after KD discontinuation. Other lipids were unchanged. A total of 18 of 27 screened eligible subjects declined participation because of unwillingness to change their diet, giving a screened-eligible/enrolled patient ratio of 3.0.

We evaluated 12 adults with refractory epilepsy treated adjunctively with KD with 3:1 [fat]:[carbohydrate + protein] weight ratio with caloric restriction of 1,600 kcal/day.[24] Seizure frequency was compared between 4 months of baseline and KD treatment. Treatment lasted 4 months initially, followed by an elective open-ended treatment extension.

KD was initiated during a 4- to 5-day-long hospitalization. Subjects fasted for 24–48 hours (until urine ketones reached ≥40 mg/dL), followed by daily caloric increase to 33%, 66%, and 100% of caloric target.

Three subjects stopped the diet prematurely: 2 for social reasons, 1 for lack of efficacy. Nine of 12 subjects completed the initial 4 months of treatment. All elected to continue the diet. Six subjects (50%) continued the diet for ≥1 year, 3 for ≥2 years, and 1 for ≥3 years, still continuing at 5 years to date.

Ten of 12 subjects improved, one did not change, and one worsened. Seizure frequency for the 11 subjects treated for >1 week declined by 38% for KD months 1–4. One patient (8%) became seizure-free. Thirty-three percent had >75% seizure reduction. Forty-two percent had >50% seizure reduction. Efficacy was similar for the entire treatment duration. Seizure-free months increased from 20% during baseline to 56% during both study phases.

Five subjects had PGE; 7 had focal epilepsy. Mean overall seizure frequency reduction was 30% for LRE and 68% for PGE (table 3) but the sample was too small for a meaningful comparison.

Three of 4 subjects with ≥75% seizure reduction stopped the diet, after 1.5, 8, and 18 months, because of diet restrictiveness. In all 3, seizures returned to pretreatment frequency.

Response to treatment was rapid. The full effect occurred during the first month of treatment. In 4 subjects with daily absence/myoclonic seizures, response reached its full extent within 4 days of KD initiation.

Two subjects without improvement on 3:1 diet (both compliant) increased the [fat]:[carbohydrate + protein] weight ratio to 4:1 after 2 months. One did not improve and stopped the diet. The other became seizure-free and has continued the diet for 5 years to date.

Diet compliance was evaluated with daily urine ketone body and monthly serum β-hydroxy-butyrate (BHB) levels.[24] Seven of 12 subjects were fully compliant. Four were partially compliant. One was noncompliant and stopped KD after 4 days. The diet was well-tolerated. No subjects discontinued treatment because of side effects. Side effects were mild and included nausea (n = 2), isolated vomiting (2), diarrhea (2), constipation (1), and abdominal cramps (1). Twenty-five percent of subjects had mild intermittent hunger. All subjects lost weight.

Mean serum cholesterol level increased by 21% from 213.5 mg/dL to 257.8 mg/dL (table 3). Three patients experienced pronounced hypercholesterolemia, which responded to statin therapy. Other lipid levels did not change significantly. In patients with hypercholesterolemia on KD, cholesterol returned to prestudy baseline within 3 months of stopping the diet; statins started during the diet were stopped after KD was discontinued.

Recruitment into the study was difficult. Twelve subjects were enrolled. Twenty-three screened eligible patients declined participation because of reluctance to give up regular diet (n = 17), complexity of the

diet (n = 5), and cost. Ratio of screened-eligible to enrolled subjects was 35/12 (2.92).

The last study evaluated 15 adults treated for 12 months with KD (n = 2), medium chain triglycerides (n = 11), or both (n = 2, started on MCT and switched to KD because of gastrointestinal side effects).[25] Ten of 15 subjects stopped treatment before study completion, mainly due to lack of efficacy. Of the 5 completers, 2 had 50%–90% seizure reduction, 3 <50%. Two of those 5 patients continued the treatment long term. Urinary ketosis was achieved in only 40% of subjects at study completion, and serum BHB levels were low. Common side effects were vomiting, diarrhea, constipation, weight loss, and fatigue. One patient developed nephrolithiasis after >1 year of treatment. Two had hyperlipidemia.

MODIFIED ATKINS DIET KD is restrictive, not very palatable, and logistically difficult to execute. Food shopping and meal preparation require counting of carbohydrate, fat, and protein grams, calculation of the ratios, and weighing of foods in meal preparation. This is time-consuming and complicated. Patients with refractory epilepsy are often of lower socioeconomic status and are unable to execute the diet.

Atkins diet is based on a similar principle as KD, namely high fat and low carbohydrate content. However, it is less restrictive. Carbohydrates are restricted to 20 g/day during the induction phase[26] of 2–4 weeks, with subsequent increase to a range of 25–90 g/day. Consumption of fats is encouraged, but neither fat nor protein grams are specified or counted. The diet does not require weighing of food. It has approximately a 0.9:1 [fat]:[carbohydrate + protein] weight ratio, with approximately 50% of calories derived from fat, as opposed to 87%–90% in KD.

The Atkins diet has been modified (MAD) for use in patients with intractable epilepsy as an easier-to-execute variety of KD.[27] Unlike the Atkins diet, MAD restricts carbohydrate intake to 15–20 g/day indefinitely. MAD has approximately 1:1 [fat]:[carbohydrate + protein] weight ratio. It induces ketosis. It is less complex and more palatable than traditional KD and may therefore have greater compliance potential in adults.[28] Its efficacy in children with refractory epilepsy is similar to KD.[2,4,5]

Five studies have evaluated MAD in adults with refractory epilepsy. All were prospective, open-label, uncontrolled studies. Their results are summarized in table 2.[28–32]

The first study evaluated 8 adults treated for 6 months with MAD. Carbohydrate intake was 20 g/day. Only 3/8 patients completed the study, 1 with seizure reduction of >50%.[29]

A larger study evaluated 30 adults. Initial carbohydrate restriction was 15 g/day. Initial treatment period was 6 months, followed by open-ended extension.[28] Fifty-three percent of subjects stopped treatment before 6 months: 56% due to lack of efficacy, 38% due to diet restrictiveness. All subjects who completed the 6-month study elected to continue the diet. Thirty-three percent of all subjects achieved >50% seizure reduction at 6 months; 13% >75% seizure reduction. One patient (3%) became seizure-free. In those with seizure reduction, the median time to improvement was 2 weeks.

Side effects included lethargy (n = 1), transient leg swelling (n = 1), and increased cholesterol, by 7% from baseline mean 187 mg/dL to 201 mg/dL (table 3).

Eighty-five percent of patients lost weight, with mean weight loss of −6.8 kg, body mass index (BMI) reduction from 28.3 to 26.4 kg/m^2, and reduction of obesity (BMI >30) from 37% of patients to 23%. There was a correlation between BMI decrease and efficacy at 3 months, but no significant difference in caloric reduction between subjects with >50% vs <50% seizure frequency reduction.

All patients on the diet for at least 1 week became ketotic. Sixty-one percent had moderate to large ketosis at 1 month (40–160 mg/dL), but only 13% at 6 months. There was correlation between level of ketosis and seizure reduction at 1 month but not at 3 and 6 months. Forty percent of patients increased carbohydrate content from the initial 15 g/day to 20 g/day at 1–3 months of the study because of restrictiveness of the 15 g/day regime. None had worsening of seizures or of ketosis. There was no difference in efficacy between daily carbohydrates of <20 g/day vs ≥20 g/day.

A similar MAD study was performed more recently with carbohydrate restriction of 20 g/day.[30] Treatment lasted 12 months. One hundred thirty-one adults were screened but only 18 consented to participate (screened/enrolled ratio of 7.2), because of diet restrictiveness and cost. Four patients (22%) dropped out, all during the first 6 months, because of cost, logistical difficulties, and carbohydrate restriction. Only 17% of patients experienced >50% seizure reduction. None became seizure-free. Ketosis was unrelated to diet efficacy and decreased over time. Only 2 of the 3 patients with a >50% reduction in seizure frequency were ketotic (both trace only).

There were no side effects except for weight loss. Mean weight decreased by −10.9 kg, and mean BMI from 31.6 to 27.8. Sixty-four percent of patients who completed the study were obese at baseline vs 29% at study end. There was no correlation between weight or BMI reduction and change in seizure frequency.

Cholesterol levels did not change significantly. Triglyceride levels declined from 1.22 to 0.9 mmol/L.

Another study evaluated MAD supervised by e-mail rather than personal visits in adults with pharmacoresistant epilepsy.[31] Treatment lasted 3 months. Adults self-administered a 20 g carbohydrate/day

MAD, with no clinic visits. Twenty-five participants consented but only 22 started treatment.

Thirty-six percent of patients stopped treatment before study completion. Twenty-seven percent of patients had >50% seizure reduction including 14% with >90% seizure reduction, including one patient who became seizure-free. Twenty-seven percent of participants chose to continue the diet after study completion. Median time to seizure improvement was 7 days. Side effects included diarrhea (2), gastroesophageal reflux (1), flatulence (1), abdominal pain (1), weakness (1), menstrual irregularities (1), and increased seizure frequency (1). Mean weight loss was −3.1 kg. In 9 patients with laboratory values, mean cholesterol level increased by 34% (table 3).

Most recently, a small group of adolescent (n = 1) and adult (n = 6) patients with refractory juvenile myoclonic epilepsy were treated adjunctively with MAD.[32] At 3 months of treatment, 4/7 (57%) patients had ≥50% seizure frequency improvement. Forty-three percent of patients had ≥90% seizure reduction, and 29% became seizure-free. Three patients continued with the diet long term, 16–40 months and ongoing at the time of publication. Several patients found the diet difficult to adhere to. Side effects included weight loss in 5 patients. One patient had hypercholesterolemia, which reversed after dietary counseling.

KD TREATMENT OF STATUS EPILEPTICUS

Refractory status epilepticus (RSE) has high mortality and morbidity and no good treatment options. There has been increasing interest in potential use of KD in the treatment of RSE.

Approximately 50 children with RSE treated with KD have been reported.[33] There have been 14 published adult cases of KD treatment of RSE (table 4).[34–38] All have been retrospective analyses (Class IV evidence). Two reports included single cases,[34,36] one 2 cases,[35] and one 10 cases,[38] including 1 previously published case.

Of the isolated cases, in one patient, KD was started 1 month after status epilepticus began concomitantly with initiation of lamotrigine; seizures stopped after 7 days but the patient died several months later.[34] In another case, KD was started after 15 days of status epilepticus. Seizures stopped after 4 days, with full recovery.[36] In 2 cases of nonconvulsive status epilepticus, KD was started 101 days into status epilepticus in 1, with seizures stopping 11 days later, and after 18 days of status epilepticus in another, with seizures stopping 8 days later.[35]

In the only case series of n ≥ 2, 10 patients with RSE were treated with adjunctive KD. Three had paraneoplastic encephalitis, 4 encephalitis of unknown etiology, and 1 each anoxia, neurocysticercosis, and cortical dysplasia.[38] Details of status epilepticus

Table 4 Summary of studies of adjunctive treatment of refractory and super refractory status epilepticus with ketogenic (or MAD) diet in adults with refractory epilepsy[34–36,38]

Reference	Subjects, n	Days of SE before KD	Days from KD start until SE end	Final outcome	Etiology	AE
Bodenant et al.[34]	1	31	7	Death	Epileptic encephalopathy, pneumonia	0
Nam et al.[36,a]	1	15	4	Normal	Viral encephalitis	GER
Wusthoff et al.[35]	2[1]	101	11	Focal deficit	Rasmussen encephalitis	Acidosis
		18	8	Normal	Viral encephalitis	
Thakur et al.[38,b]	10[c]	57	1	Rehab	Encephalitis, unknown etiology	↑TG
		17	2	Rehab	Paraneoplastic encephalitis	0
		45	3	Respiratory care unit	Cortical dysplasia	0
		19	3	Rehab	Encephalitis, unknown etiology	↑TG
		24	5	Rehab	Encephalitis, unknown etiology	0
		13	7	Death	Anoxia	0
		17	12	Rehab	Neurocysticercosis	0
		38	31	Rehab	Paraneoplastic encephalitis	Acidosis
		2	1	Rehab	Encephalitis, unknown etiology	0
		60	NA	Death	Paraneoplastic encephalitis	Cardiac arrest
Total	14					

Abbreviations: AE = adverse events; GER = gastroesophageal reflux; KD = ketogenic diet; MAD = modified Atkins diet; NA = not available; SE = status epilepticus; TG = triglycerides.
[a] The patient had received 5 standard antiepileptic drugs but no anesthesia before KD initiation.
[b] Ten of 14 subjects have insufficient clinical description to determine seizure or status epilepticus type.
[c] The article includes one previously published case.[34]

type, anesthetics, and AEDs used at the time of KD initiation were not reported. The authors reported that "90% had resolution of status epilepticus." However, in only 4 of the 9 "responders" did seizures stop soon after KD initiation to suggest a causal effect of KD on status epilepticus cessation. In these 4 patients, status epilepticus duration before treatment vs time to seizure cessation after KD initiation was, in days, 57/1, 17/2, 45/3, and 19/3. In the other 5, the relationship was not clearly causal: 38/31, 17/12, 13/7, 2/1, and 24/5. Adverse events included hyperlipidemia (2), acidosis (1), and cardiac death during status epilepticus (1). Long-term outcomes were not reported, except for 2/10 cases of death, including 1 "responder" with persistent coma after status.

Other observed side effects have included gastroesophageal reflux, and, in children, aspiration pneumonia, constipation, and 1 case of fatal propofol infusion syndrome[39] (propofol may impair fatty acid oxidation, which causes propofol infusion syndrome).

Due to the small numbers, interpretation of these reports is difficult. In case reports or small series, there is a bias to publish positive results. It is not known how many patients with RSE have received KD and failed. We know of several cases of RSE treated unsuccessfully with KD: none was published. The data are retrospective. In most cases, details of pre-KD management, including changes in AEDs and doses in relation to KD initiation, are lacking, as are status epilepticus features and clinical outcomes other than seizure cessation. Most importantly, in many cases there is a long time lag between KD initiation and seizure cessation: ≥1 week in 6 of the 13 reported "responders." This makes a causal relationship between KD and status epilepticus cessation tenuous, and raises the question of whether seizures may have stopped spontaneously (burned out status), as a result of other intervention, or due to KD.

OVERVIEW Data on dietary treatment in adults with epilepsy are limited.[40]

KD and MAD adjunctive treatment of refractory epilepsy in adults shows modest efficacy, although in some patients the effect can be remarkable. Across all studies, 32% of KD-treated patients and 29% of MAD-treated patients achieved ≥50% seizure reduction, including 9% and 5%, respectively, of patients with >90% seizure reduction. There is a suggestion that PGE may respond better than LRE in the few studies that have data by epilepsy type, but the numbers are too small for meaningful evaluation. The effect persists long term, but does not outlast the treatment.[20] The 3:1 and 4:1 [fat]:[carbohydrate + protein] ratio KD variants may be similarly effective.[21,22,24]

The anticonvulsant effect occurs quickly with both diets, within days to weeks.[24,28] It does not appear to be related to level of ketosis, amount of carbohydrate intake (in MAD), or weight loss (MAD). At present, there are no clinical or biochemical predictors of treatment responsiveness. Side effects of both diets are benign and similar. The most serious side effect, hyperlipidemia, reverses readily with treatment discontinuation. Weight loss is the most common side effect in both diets, and may be used to advantage in patients with comorbid obesity.

Potential barriers to large-scale use of the diets in adults include low rate of acceptance of the diet and high rates of diet discontinuation, similar in KD and MAD. For both diets, patients are reluctant to try the treatment. The eligible screened/enrolled subject ratios range from 2.9 to 7.2.[23,24,30] Refusal to participate is commonly due to restrictiveness and complexity of the diet.[22–24,30] This is greater in KD, although in motivated patients it may not be an obstacle. The low likelihood of long-term adherence to the diet is more of a problem. In both KD and MAD studies, retention was poor. Fifty-one percent of KD-treated and 42% of MAD-treated patients stopped the diet before study completion. Most patients, even those with 75%–100% seizure frequency reduction, eventually stop the diet because of culinary and social restrictions.[22,24] Although easier to administer than KD, MAD is still not easy to adhere to long term. Epilepsy is a chronic disease. If the treatment cannot be adhered to long term (i.e., indefinitely), it may be of limited utility.

That said, in patients willing to try dietary treatment, the effect is seen quickly, giving patients the option whether to continue the treatment long term.

For status epilepticus, current data do not provide evidential basis for KD use. Until more data are available, KD should be used in status epilepticus only as a last resort.[41]

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DISCLOSURE

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