HHS Public Access

Author manuscript

Semin Neurol. Author manuscript; available in PMC 2021 December 01.

Published in final edited form as:

Semin Neurol. 2020 December ; 40(6): 719–729. doi:10.1055/s-0040-1719077.

Ketogenic Diet Therapies for Seizures and Status Epilepticus

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Abstract

Ketogenic diet therapies are high-fat, low-carbohydrate diets designed to mimic a fasting state. Although initially developed nearly one century ago for seizure management, most clinical trials for the management of drug-resistant epilepsy in children as well as adults have been conducted over the last 3 decades. Moreover, ketogenic diets offer promising new adjunctive strategies in the critical care setting for the resolution of acute status epilepticus when traditional antiseizure drugs and anesthetic agents fail. Here, we review the history of ketogenic diet development, the clinical evidence supporting its use for the treatment of drug-resistant epilepsy in children and adults, and the early evidence supporting ketogenic diet feasibility, safety, and potential efficacy in the management of status epilepticus.

Keywords

ketogenic diet; modified Atkins diet; epilepsy; refractory status epilepticus

History of Ketogenic Diet Therapies and Their Evolution Over Time

Diet therapy in the form of food restriction has been used to treat epilepsy since as early as 400 BC when contemporaries believed that certain foods could exacerbate or cause seizures.[1] Moreover, reference is made in the bible of a patient with epilepsy being cured through "prayer and fasting."[2] Despite early reports of seizure reduction in patients treated with high-fat, carbohydrate-limited diets in the 1920s, evidence-based studies examining diet therapy were scarce following the introduction of antiseizure drugs (ASDs) until the 1990s when studies re-emerged demonstrating its efficacy in patients with drug-resistant epilepsy (DRE) and particular pediatric epilepsy syndromes.[3-5] There has subsequently been increasing interest worldwide in the use of ketogenic diet therapies (KDTs) to manage DRE, as an estimated 19.5 million people with epilepsy have seizures not well controlled by medications.[6] Similarly, KDT may offer a needed adjunctive therapy in the management of status epilepticus in critical care settings, as mortality and long-term neurological morbidity rates remain high and standardized treatment algorithms are lacking.[7,8]

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Conflict of Interest

Dr. Cervenka reports grants and personal fees from Nutricia North America, grants from Vitaflo, personal fees from Demos Health, grants from William and Ella Owens Medical Research Foundation, grants from BrightFocus Foundation, and personal fees from Glut1 Deficiency Foundation, outside the submitted work.

Dr. McDonald reports personal fees from Nutricia North America, outside the submitted work.

A ketogenic diet (KD) is defined as a high-fat, low-carbohydrate diet that induces ketone body production in the liver through fat metabolism. The goal is to mimic a fasting state without depriving the body of necessary calories to sustain growth and development.[9,10] The classic KD (CKD) is composed of a macronutrient ratio of 4:1 (4 g of fat to every 1 g of protein plus carbohydrates combined), thus shifting the predominant caloric source from carbohydrate to fat. Fatty acids metabolized by the liver produce the ketone bodies acetoacetate (which spontaneously converts to acetone) and β-hydroxybutyrate, which enter the bloodstream and are utilized by organs including the brain where they are further metabolized in mitochondria to generate energy. With KD use, ketone bodies become the major fuel source for the central nervous system, replacing glucose. Ketosis, indicated by elevated ketone concentrations in the urine or serum, is used as a marker of early compliance following diet initiation, but levels of ketosis are not necessarily predictive of seizure reduction.[11,12] To increase flexibility and palatability, less strict KD variants have been developed in recent years, including lower ratio KDs, the modified Atkins diet (MAD), the low glycemic index treatment (LGIT), and combining these diets with medium-chain triglyceride (MCT) oil. KDs with lower ratios of 3:1, 2:1, or 1:1 (referred to in some studies as modified KDs) are typically chosen based on patient age, individual tolerability, goal level of ketosis, and protein requirements.[13] The MAD, introduced into practice in 2003, restricts net carbohydrates to a 10 to 20 g/day limit (most often 10 g in children and 20 g in adults), which is roughly equivalent to a ratio of 1 to 2:1 of fat to protein plus carbohydrates.[14,15] The LGIT, developed in 2005, specifies a limit of 40 to 60 g daily of carbohydrates with glycemic indices <50, and approximately 60% of dietary energy derived from fat and 20 to 30% from protein.[16] While the CKD utilizes mainly large and some short-chain triglycerides and MCTs in a mix of fat types, the MCT variant KD (MCT-KD) incorporates approximately 60% of calories from MCTs provided in coconut and/or palm kernel oil as a fat supplement and allows for greater carbohydrate and protein intake than even a lower-ratio KD,[17] which can improve compliance. However, due to gastrointestinal side effects including nausea, diarrhea, and cramping, strategies have been utilized to gradually increase MCT fraction from 30–40% up to 60% as tolerated.

Ketogenic Diet Therapies for Drug-Resistant Epilepsy in Children and Adults

Initial clinical studies and additional evidence since the turn of the century support KDT use in epilepsy management, with modern research reporting efficacy defined by the proportion of patients achieving ≥50% seizure reduction (defined as responders). In the pediatric population, a 2016 Cochrane library review[3] analyzed the results of seven randomized controlled trials (RCTs) of KDT efficacy in 427 children and adolescents with epilepsy (summarized in ►Table 1).[18-24] Of those studies comparing KDT to usual diet, 3-month responder rates (RR) ranged from 38 to 52% in the diet arms, compared with 6 to 11.5% in the control arms, respectively.[21,23] Of studies comparing different KD variants, 3-month RRs as high as 85% were observed for a 4:1 ratio CKD compared with 72% on a 3:1 ratio KD and as high as 60% for a 10 g restricted MAD, compared with 10% on a 20 g restricted MAD, and these differences were statistically significant.[19,20] Adverse effects were fairly consistent across different KDT interventions, with gastrointestinal symptoms most

commonly reported.[3] Since the publication of the 2016 Cochrane review, there have been four additional RCTs in the pediatric population either evaluating KDTs compared with usual diet or comparing two KDT variants (also summarized in ►Table 1).[25-28] RRs of 45 to 56% were observed in the KDT arms when compared with controls,[26,28] and no significant difference in RRs was observed in various diet comparisons (KD vs. MAD; CKD vs. MCT-KD).[25,27] Overall, KDT has been shown to result in a 50% or greater reduction in seizure frequency in an estimated 50% of children and adolescents with epilepsy. This is comparable to RRs seen in clinical trials for recently developed ASDs brivaracetam (RRs for doses ranging from 50 to 200mg/d were 34.2–39.5%),[29] eslicarbazepine (RRs for doses 800 and 1,200mg/d were 30.5 and 42.6%, respectively),[30] and perampanel (RR of 64.2% for 8mg/d dose)[31] in epilepsy patients with seizures uncontrolled by one to three ASDs.

In the adult population, a 2015 systematic review and meta-analysis reviewed 12 observational studies using CKD, MAD, and MCT-KD in 270 patients with DRE. They found a combined efficacy rate of 52% for CKD and 34% for MAD.[32] A similar 3-month RR of 39% was observed in the largest observational study, published after the 2015 review, of 101 adult DRE patients naive to diet therapy who subsequently began MAD.[33] Moreover, recent RCTs have evaluated MAD efficacy in adults with DRE (summarized in ►Table 1).[34-36] An RCT in Iran compared RRs in patients with focal or generalized epilepsy randomized to 2 months of MAD or habitual diet and found 35.5% (12/34) efficacy in the MAD group compared with 0% in the control group, a difference that was statistically significant.[34] A Norwegian study randomized 75 adults with drug-resistant focal epilepsy to either 12 weeks of treatment with MAD (16 g carbs/d) or continuation of their habitual diet.[35] There was no significant difference between the diet and control groups in seizure frequency after the intervention ($p = 0.21$); however, more patients in the diet group achieved 25 to 50% reduction in seizures compared with controls ($p = 0.03$). Lastly, an American crossover RCT randomized 80 adults with drug-resistant focal or generalized epilepsy to receive treatment with either MAD alone (20 g net carbs/d) or MAD supplemented with a 4:1 ratio ketogenic formula.[36] In total, 47.5% of participants in the supplement arm were responders (≥50% reduction in seizures) and 37.5% in the diet alone arm, with no significant difference between groups ($p = 0.498$). However, there was a trend for higher continuation of MAD beyond the study period in the supplement arm (14/35, 40%) compared with the diet alone arm (7/36, 19%; $p = 0.072$). Collectively, the most common adverse effects noted in the RCTs of MAD use in adults were gastrointestinal symptoms that included nausea/vomiting, reflux, constipation, and diarrhea, as well as a change or increase in seizure pattern/semiology.[34-36] Overall, consistent with published RCTs, adult observational studies of KDTs demonstrate RRs of 22 to 70% for CKD and 12 to 67% for MAD,[32,37,38] with some suggestion of increased efficacy in adults with generalized rather than focal epilepsy.[39,40]

Ketogenic Diet Therapies in the Management of Status Epilepticus

Status epilepticus (seizure lasting longer than 5 minutes or recurrent seizures without return to neurologic baseline between seizures) may continue despite appropriate first- and second-line ASD treatment and has been termed refractory status epilepticus (RSE). Current treatment algorithms utilize various intravenous anesthetic agents for 24 hours or more to

suppress RSE if second-line drugs do not stop seizures. If status epilepticus continues or recurs 24 hours or more after the initiation of treatment with anesthetic agents, patients are diagnosed with super- RSE (SRSE).[41] As both RSE and SRSE carry high rates of morbidity (ranging from 30 to 61% in children and adults) and mortality (ranging from 16 to 44% in children and adults),[7,41-44] KDTs offer a needed adjunctive management strategy. KDT is relatively easy to start, monitor, and maintain in the critical care setting, without hemodynamic instability seen with anesthetic drugs. In addition there is growing preclinical evidence that KDTs may undermine the pathophysiology of RSE at several levels, including receptor trafficking, neurotransmitter localization and release, mitochondrial dynamics in the face of oxidative stress, and modulation of proinflammatory cytokine expression and release.[45-55] Such a multifaceted approach may be particularly useful in the treatment of new-onset RSE (NORSE) and febrile infection-related epilepsy syndrome (FIRES). NORSE is a clinical presentation described in patients without epilepsy or a relevant preexisting neurological disorder, who present with RSE without an identifiable acute cause or active structural, toxic, or metabolic cause, often with a suspected or later diagnosed autoimmune etiology.[56,57] A subcategory of NORSE known as FIRES requires a prior febrile illness starting between 2 weeks and 24 hours prior to the onset of status epilepticus, and can present with or without fever at the onset of status epilepticus.[58] While NORSE and FIRES are relatively rare epilepsy syndromes, they are frequent in the RSE/SRSE population.

Several case reports and case series over the last decade demonstrate the feasibility and, in some instances, success of KDT for resolution of RSE and SRSE in children (summarized in ►Table 2).[59-85] In the majority of patients, KDT was given via the enteral route, typically using a nasogastric or percutaneous endoscopic gastrostomy tube. However, in some cases the KDT was administered intravenously or via total parental nutrition when enteral access was not immediately available and then later converted.[78,80-82,84] The largest studies of KDT use for pediatric status epilepticus management, with ≥10 patients each, included one multicenter study[83] and three single-center studies.[74,81,85] In the first large retrospective case series, of 10 children with RSE treated with an enteral KDT, 100% (10/10) achieved ketosis in a mean of 3 days (range 2–4 days), 20% (2/10) had seizure resolution, and 50% (5/10) demonstrated 50 to 75% seizure reduction at a mean of 5 days (range 5–7 days) following diet onset.[74] The diet was discontinued within 7 days in the three children with <50% seizure reduction and adverse effects. A multicenter study including 14 children reported RSE resolution in 71% of patients (10/14) within 7 days of starting enteral 3 to 5:1 ratio KDT.[83] Although KDT in this study was not initiated until a median of 13 days of RSE (range 3–39 days), ketosis was achieved in a median of 2 days (range 0–10 days), and in 76% of patients (11/14) continuous anesthetic infusions could be weaned off within 2 weeks of KDT initiation. In the two large retrospective case series at single centers of KDT management of pediatric SRSE,[81,85] 90% of children receiving KDT treatment after a median of 18 to 23 days of SRSE achieved ketosis at a median of 3 to 6 days and experienced resolution of SRSE (90%[81] and 60%[85]) or >50% seizure reduction (30%[85]) at a median of 7 days after diet onset. Common adverse effects reported with the use of KDT for RSE/SRSE in studies of five or more patients have included metabolic derangements like acidosis and hypoglycemia, hyperlipidemia and elevated triglycerides, and gastrointestinal

symptoms similar to those reported in the outpatient setting, while pancreatitis and nephrolithiasis have been rare.[86]

Since the first report of KD use for SRSE in an adult published in France in 2008,[87] additional case reports as well as retrospective and prospective case series have continued to support the feasibility and potential efficacy of KDTs for management of RSE and SRSE in adults (summarized in ►Table 3).[63,67,85,88-99] The largest of these studies, with ≥10 patients each, included two multicenter studies and one single-center study.[92,96,98] The first, a case series of 10 adults with SRSE of median duration 21.5 days treated with KDT (9 with a 4:1 ratio CKD and 1 with a 3:1 ratio KD) at 4 medical centers showed successful cessation of status epilepticus in 100% of patients who achieved ketosis (9 out of 10 adults) at a median of 3 days (range 1–31 days).[92] In the largest case series of 15 adult patients treated with 4:1 ratio KDT (14 of whom completed therapy) after a median of 10 days of SRSE at four medical centers, 11 (79% of patients who completed KDT) achieved resolution of seizures in a median of 5 days (range 0–10 days).[96] In the most recent large case series of 11 adults with RSE of median duration 1 day (range 0–3 days) treated with a 3–4:1 ratio CKD at a single center, 91% of patients (10/11) achieved ketosis in a median of 1 day (range 0–5 days) and 73% of patients (8/11) showed successful resolution of RSE.[98] Collectively, adverse events reported in adults on KDTs included acidosis, hypoglycemia, hyperlipidemia, elevated triglycerides, hyponatremia, and gastrointestinal side effects. The majority of these were successfully managed with supplementation or supportive management and did not necessitate KD cessation.

While studies to date in children and adults largely support the clinical use of KDT to promote cessation of RSE and SRSE when standard measures have failed, RCTs are warranted to better establish efficacy and assess impact on mortality and long-term neurologic morbidity. Importantly, implementation of KDTs in the critical care setting requires a trained multidisciplinary team for successful administration. Not only is a dietitian or nutritionist familiar with KDT a critical member of the team, but the entire intensive care unit team (including the physicians, pharmacist, and nursing staff) needs to be aware of the dietary treatment as well as basic management principles (e.g., minimizing carbohydrates in medications, parental and intravenous fluids) to avoid inadvertently bringing the patient out of ketosis.

Ketogenic Diet Therapies: Select Epilepsy Indications, Monitoring, and Contraindications

The scientific literature to date indicates increased KDT efficacy in certain epilepsy syndromes or types. KDT is the standard treatment for glucose transporter type 1 (GLUT1) deficiency syndrome, a rare genetic condition caused by impaired glucose transport into the brain and associated with an abnormality in the gene SLC2A1.[100] Studies in patients with GLUT1 and seizures have shown up to 90% of patients with GLUT1 becoming seizure free on the CKD or MAD.[101,102] Similarly, for patients with pyruvate dehydrogenase deficiency, where KDT overcomes the deficiencies in the catalytic component of the mitochondrial enzyme pyruvate dehydrogenase complex by providing an alternative source of acetyl

coenzyme A, KDT is considered first-line treatment.[103-105] There is also general consensus agreement that patients with infantile spasms, tuberous sclerosis complex, Dravet syndrome, Angelman syndrome (particularly with the LGIT), complex I mitochondrial disorders, Ohtahara syndrome, and myoclonic-astatic epilepsy (Doose syndrome) benefit from a trial of diet therapy, as studies have consistently shown KDTs as more beneficial (>70%) than the expected 50% RR.[106-109] In addition, high response rates and seizure freedom have been observed in adolescents and adults with juvenile myoclonic epilepsy, with two-thirds of adults showing ≥50% seizure reduction and one-sixth of adults seizure-free in two separate small case series.[39,110] Similarly, a trend for increased benefit of KDT has been suggested for patients with symptomatic generalized epilepsy compared with patients with focal epilepsies.[111]

Based on reviews and protocols establishing the safety, feasibility, and efficacy of KDTs in treating DRE and RSE/SRSE,[33,75,82,92,96,109] recommended baseline measures include height and weight, serum fasting lipid profile, comprehensive metabolic profile, complete blood count, urine ketones and urine pregnancy screen (in premenopausal women), and levels of vitamin D. An assessment of food availability, preferences, allergies, and intolerances is also typical in the outpatient clinic setting. Suggested follow-up testing includes urinalysis, fasting lipid profile, urine calcium and creatinine, serum levels of total and free carnitine, zinc, selenium, vitamin D, and ASD levels. During KDT maintenance in RSE/SRSE management, baseline amylase and lipase, point-of-care glucose testing to maintain serum glucose >30mg/dL in children and 50mg/dL in adults, urine ketones and serum β-hydroxybutyrate measurements, and comprehensive metabolic profile testing to maintain normal serum bicarbonate levels are additionally warranted. Multivitamin, calcium, and vitamin D supplementation should be co-administered at diet onset if the ketogenic formula or foods used are not nutritionally complete.

Contraindications for adjunctive KDT include severe metabolic or hemodynamic instability, liver failure, inability to tolerate enteral feeds, acute pancreatitis, as well as pregnancy as possible teratogenic effects of KDT are largely unknown.[96,112] In addition, patients receiving any propofol infusion within 24 hours may not be candidates for KDT based on a prior report of fatal propofol infusion syndrome in a patient receiving concomitant KDT for RSE.[113] KDT use is also contraindicated in patients with rare metabolic disorders, including primary carnitine deficiency, carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency, porphyria, and other disorders of fatty acid transport and oxidation.[109] These diagnoses are typically made in early childhood and thus are not typically a major consideration in adults presenting with new-onset epilepsy or status epilepticus, but should be considered in the pediatric population.

Conclusions

Current evidence supports the use of KDTs as adjunctive therapy in seizure management. Clinical studies, including RCTs, demonstrate the feasibility, tolerability, and efficacy of the CKD and the MAD in the treatment of DRE in both children and adults. Growing evidence from case reports and case series highlight the feasibility, safety, and potential efficacy of

KDT, particularly administered through the enteral route, in the management of RSE in the pediatric and adult population. However, RCTs in the critical care setting are needed as well as assessments of whether KDT use decreases mortality or long-term morbidity associated with RSEC and SRSE.

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Semin Neurol. Author manuscript; available in PMC 2021 December 01.

Table 1

Summary of published randomized controlled trials of ketogenic diet therapy efficacy for seizure management in children and adults

Population	First author (year)	Study design	Subjects, *n*	Diet	Comparison treatment	Duration (mo)	Significant study results (RR)	KDT attrition % (number; reason)
Children	Bergqvist (2005)[18]	RCT	48	24 CKD (4:1 ratio), 24–48 h fasting	24 CKD (4:1 ratio), nonfasting	3	No difference in RR between groups (58 vs. 67%)	13% (6/48; inefficacy, side effects)
	Kossoff (2007)[19]	RCT crossover	20	10 MAD (10 g/d)	10 MAD (20 g/d)	3 (of each treatment), 6 (total study)	60% (6/10) RR in 10 g MAD arm compared with 10% (1/10) in 20 g MAD arm @ 3 months; no difference between groups at 1 or 6 months	20% @ 3 months (4/20; did not start or stopped diet)
	Seo (2007)[20]	RCT	76	40 CKD (4:1 ratio)	36 KD (3:1 ratio)	3	85% (34/40) RR in 4:1 KD arm compared with 72% (26/36) RR in 3:1 KD arm	16% (12/76; intolerance, GI and other side effects)
	Neal (2008)[21]	RCT	145	37 CKD (3–4:1 ratio) 36 MCT-KD (45% fat content)	72 usual diet	3	38% (28/73) RR in diet arm compared with 6% (4/72) in control arm; also diet arm with lower mean percentage of baseline seizures	26% (19/73; did not start, food refusal, too restrictive, increased seizures, side effects)
	Neal (2009)[25]	RCT	145	73 CKD (3–4:1 ratio)	72 MCT-KD (40–45% fat content)	12	No difference in RR or mean percentage of baseline seizures between groups at 3, 6 or 12 months	35% @ 3 months (51/145; did not start or stopped for increased seizures, food refusal, or side effects)
	Raju (2011)[22]	RCT	38	19 CKD (4:1 ratio)	19 KD (2.5:1 ratio)	3	No difference in RR between groups (58 vs. 63%)	16% (6/38; inefficacy, food refusal, nonacceptance by family)
	Sharma (2013)[23]	RCT	102	50 MAD (10 g/d)	52 usual diet	3	52% RR in MAD arm compared with 11.5% RR in control arm; also diet arm with lower mean percentage of baseline seizures	8% (4/50; stopped diet early)
	El-Rashidy (2013)[24]	RCT	40	10 CKD (4:1 ratio) 15 MAD (10 g/d→ <10% carb)	15 usual diet	3, 6	KD arm had a greater rate of change in seizure frequency than the MAD arm, and both diet groups had greater rate of change in seizure frequency than control arm	16% @ 3 months (4/25; weight loss, intolerance)
	Sharma (2016)[26]	RCT	81	41 MAD (10 g/d) using simplified instructions	40 usual diet	3	56% (23/41) RR in diet arm compared with 8% (3/40) RR in control arm	5% (2/41; food refusal, side effects)
	Kim (2016)[27]	RCT	104	51 CKD (4:1 ratio)	53 MAD (10 g/d→ <10% carb)	6	No difference in RR between groups (39 vs. 36%); more seizure free @ 3 months on KD than on MAD if age 1 to <2	33% (34/104; inefficacy, intolerance, side effects)
	Lambrechts (2017)[28]	RCT	57	29 KDT (MCT-KD, CKD, or mixed)	28 usual diet	4	45% (13/29) RR in KD arm compared with 14% (4/28) RR in control arm	21% (6/29; improved seizure, change in seizure pattern, GI side effects)

Population	First author (year)	Study design	Subjects, *n*	Diet	Comparison treatment	Duration (mo)	Significant study results (RR)	KDT attrition % (number; reason)
Adult	Zare (2017)[34]	RCT	66	34 MAD (15 g/d)	32 usual diet	2	35% (12/34) RR in MAD arm compared with 0% in control arm.	35% (12/34; stopped diet)
	Kverneland (2018)[35]	RCT	75	37 MAD (15–20 g/d)	38 usual diet	3	No difference in RR between groups (8 vs. 5%); more patients with 25–50% seizure reduction in diet group	35% (13/37; did not start diet, increased seizures)
	McDonald (2018)[36]	RCT crossover	80	40 MAD (20 g/d) + ketogenic formula supplement daily	40 MAD alone	1 (of each treatment), 2 (total study)	No difference in RR between groups (55 vs. 52%), but trend for continued diet use in supplement arm (43 vs. 17%)	30% (24/80; did not start / stopped diet or supplement, change in seizure medication)

Abbreviations: carb, carbohydrate; CKD, classic ketogenic diet; d, day; g, grams; GI, gastrointestinal; KDT, ketogenic diet therapy; MAD, modified Atkins diet; MCT-KD, medium chain triglyceride-KD; NR, not reported; RCT, randomized controlled trial; RR, responder rate, defined as proportion of patients with ≥50% seizure reduction.

Table 2

Summary of published studies of adjunctive KDT for refractory and super-refractory status epilepticus in children (age < 18 years)

First author (year)	Subjects, *n*	Etiology	KDT	Time to diet start (days)	Time to ketosis (days)	Time to SE response (days)	Response%	AE
François (2003)[59]	6	Refractory SE	KD	8–75	Mean 2	Mean 2 or NA	50	NR
Mikaeloff (2006)[60]	2	Epileptic encephalopathy	KD	53 or NR	NR	2 or NA	50	NR
Chevret (2008)[61]	1	Febrile refractory SE	KD	NR	NR	NA	0	NR
Schrader (2009)[62]	2	1 FCD, 1 Rasmussen's syndrome and FCD	KD	NR	NR	NA	0	NR
Villeneuve (2009)[63]	4	SWS, 1 encephalitis, cryptogenic	KD	2–14	NR	1–10	75	NR
Kumada (2010)[64]	2	1 heterotopia, 1 frontal lobe epilepsy	MAD	NR	2–3	10–21	100	NR
Nabbout (2010)[65]	9	9 FIRES	KD	4–55	2–4 (mean 2.8) or NA	4–6 (mean 4.8) or NA	78	NR
Ismail (2011)[66]	1	FIRES	KD	90	NR	10	100	NR
Nam (2011)[67]	4	4 FIRES	KD	30–420 (mean 30)	NR	3–18 (median 8)	50, 50[a]	4 constipation, 2 GER, 1 ↑TG
Vaccarezza (2012)[68]	5	3 FIRES, 2 DRE	KD	Mean 32	NR	NR	80	NR
Sort (2013)[69]	3	1 FIRES, 1 mitochondrial, 1 HHES	KD	6–83	1–12	1–13 or NA	66	1 ↑TG
Caraballo (2013)[70]	2	2 FIRES	KD	NR	NR	NR	0, 50[a]	NR
Gedik (2014)[71]	1	Meningoencephalitis	KD	27	NR	NA	0	NR
Barros (2014)[72]	1	NMDA	KD	NR	NR	NA	0	NR
O'Connor (2014)[73]	5	1 POLG, 1 mitochondrial, 3 unknown	KD	4–22	2–8	2–8 (mean 5)	100	0
Caraballo (2014)[74]	10	1 NMDA, 2 FCD, 1 hemimegalencephaly, 6 unknown	KD	NR	2–4 (mean 3)	5–7 (mean 5) or NA	20, 50[a]	2 pancreatitis, 1 vomiting and hypoglycemia
Cobo (2015)[75]	4	1 TSC, 3 cryptogenic epilepsy	KD	19–67	<10	2–8 or NA	0, 75[b]	1 nephrolithiasis, 1 constipation and GER, 1 hypoglycemia
Fung (2015)[76]	4	1 NORSE, 1 VGKC encephalitis, 1 FIRES, 1 limbic encephalitis	KD	12–21 (median 17.5)	4–5	5 or NA	25	1 vomiting
Incecik (2015)[77]	1	DRE	KD	NR	NR	NA	0	NR

First author (year)	Subjects, *n*	Etiology	KDT	Time to diet start (days)	Time to ketosis (days)	Time to SE response (days)	Response%	AE
Lin (2015)[78]	1	Focal epilepsy	KD (IV → EN)	2	1	6	100	Weight loss, diarrhea
Caraballo (2015)[79]	2	Refractory myoclonic SE	KD	21–30	1	7	0, 100[a]	0
Chiusolo (2016)[80]	1	DRE	KD (IV → EN)	NR	2	NA	0	
Appavu (2016)[81]	10	2 NMDA, 2 FIRES, 1 NORSE, 1 LGS, 1 Rasmussen, 1 mycoplasma, 1 DRE, 1 NKH	KD (9 EN, 1 TPN → EN)	1–45 (median 18)	0–13 (median 6) or NA	1–19 (median 7) or NA	90	1 acidosis, hypophosphatemia, and hypokalemia
Farias-Moeller (2017)[82]	9	7 FIRES, 1 epileptic encephalopathy, 1 HLH	KD (7 EN, 1 IV, 1 IV → EN)	7–41 (median 13)	2–13 (mean 4)	7 or NA	55, 11[a]	2 ↑TG, 1 pancreatitis, hypoglycemia
Arya (2018)[83]	14	10 unknown, 1 TSC, 1 MCD, 1 FIRES	KD	3–39 (median 13)	0–10 (median 2)	7 or NA	71	2 ↑TG, 1 GI paresis
Peng (2019)[84]	7	7 FIRES	KD (2 IV → EN, 5 EN)	7–31	1–11	0–10	100	4 HLD, 3 diarrhea
Park (2019)[85]	10[c]	4 FIRES, 2 HIE, 2 Viral encephalitis, 1 hemimegalencephaly, 1 cryptogenic epilepsy	KD	3–237	2–6 (median 3)	7	60, 30[a]	4 GER, 1 nephrolithiasis, 1 acidosis, 1 ↑TG, 1 ↑ liver enzymes

Abbreviations: AE, adverse events deemed related to KDT use; DRE, drug-resistant epilepsy; EN, enteral; FCD, focal cortical dysplasia; FIRES, febrile infection related epilepsy syndrome; GER, gastroesophageal reflex; GI, gastrointestinal; HHES, hemiconvulsion-hemiplegia epilepsy syndrome; HIE, hypoxic ischemic encephalopathy; HLD, hyperlipidemia; HLH, hemophagocytic lymphohistiocytosis; IV, intravenous; KD, classic or modified ketogenic diet; KDT, ketogenic diet therapy; LGS, Lennox–Gastaut syndrome; MAD, modified Atkins diet; MCD, malformation of cortical development; NA, not achieved; NKH, nonketotic hyperglycinemia; NMDA, N-methyl D-aspartate receptor encephalitis; NORSE, new-onset refractory status epilepticus of unknown etiology; NR, not reported; POLG, mitochondrial polymerase γ related epilepsy; response %, proportion of patients who had resolution of SE; SE, status epilepticus; SWS, Sturge–Weber syndrome; TG, triglycerides; TPN, total parenteral nutrition; TSC, tuberous sclerosis complex; VGKC, voltage-gated potassium channel.

[a]Proportion of patients with ≥50% reduction in seizures.

[b]Proportion of patients successfully weaned off continuous infusions of anesthetic medications without recurrence of SE.

[c]Excludes 4 patients previously reported in Nam et al (2011).[67]

Table 3

Summary of published studies of adjunctive KDT for refractory and super-refractory status epilepticus in adults (age ≥ 18 years)

First author (year)	Subjects, *n*	Etiology	KDT	Time to diet start (days)	Time to ketosis (days)	Time to SE response (days)	Response %	Outcome	AE
Bodenant (2008)[87]	1	Epileptic encephalopathy, PNA	KD	31	NR	7	100	Death	0
Villeneuve (2009)[63]	1	Ito syndrome	KD	2–14	NR	3	100	NR	NR
Wusthoff (2010)[88]	2	Rasmussen encephalitis; viral encephalitis	KD	20, 101	8, 10	6, 11	100	Home by 1 year	2 acidosis
Nam (2011)[67]	1	Encephalitis	KD	15	NR	7	100	Functional baseline	0
Martikainen (2012)[90]	1	POLG	LGIT	4	NR	4	100	Home	0
Strzelczyk (2013)[91]	1	Lafora disease	KD[a]	16	4	4	100	Home	0
Thakur (2014)[92]	10[b]	4 NORSE, 2 NMDA, 1 LGI1, 1 anoxia, 1 FCD, 1 neurocysticercosis	KD	2–60 (median 22)	1–7	1–31 (median 3)	90	7 ARF, 1 SNF, 1 VRU, 1 death	1 acidosis, 2 ↑TG
Matsuzono (2014)[93]	1	Encephalitis	KD	155	NR	25	100	ARF	NR
Amer (2015)[94]	1	NMDA	KD	21	NR	14	100	SNF	NR
Uchida (2017)[95]	1	NMDA	KD + STP	NR	NR	60	100	NR	NR
Cervenka (2017)[96]	15	5 NORSE, 2 LGS, 3 ICH, 2 anoxia, 1 GBM, 1 encephalitis, 1 NAT	KD	2–21 (median 10)	0–16	0–10 (median 5)	73	1 home, 8 ARF, 2 SNF, 4 death	4 acidosis, 2 GI, 2 HLD, 2 hypoglycemia, 1 hyponatremia, 1 weight loss
Blunck (2018)[97]	1	ASD change in epilepsy patient	KD + SGLT2 inhibitor[c]	107	7	NA	0	Death	0
Park (2019)[85]	1[d]	FIRES	KD	37	2–6	7	0, 100[e]	Ambulatory	Nausea/vomiting
Francis (2019)[98]	11	3 TBI, 2 ICH, 2 anoxia, 1 stroke, 1 NMDA, 1 EtOH, 1 ASD nonadherence	KD	0–3 (median 1)	0–5 (median 1)	NR	73	2 home, 4 LTACH, 2 ARF, 2 SNF, 1 CM	7 acidosis, 2 hypoglycemia, 1 hyponatremia, 1 transaminitis
Prasoppokakorn (2019)[99]	1	Autoimmune encephalitis	MCT-KD[f]	56	NA	6	100	NR	0

Abbreviations: AE, adverse events deemed related to KD use; ASD, antiseizure drug; ARF, acute rehabilitation facility; CM, comfort measures; EtOH, alcohol withdrawal; FCD, focal cortical dysplasia; FIRES, febrile infection related epilepsy syndrome; GBM, glioblastoma multiforme; GI, gastrointestinal side effects (including constipation); HLD, hyperlipidemia; ICH, intracranial hemorrhage; KD, classic or modified ketogenic diet; LGI1, leucine-rich, glioma-inactivated 1 encephalitis; LGIT, low glycemic index treatment; LGS, Lennox–Gastaut syndrome; LTACH, long-term acute care hospital;

MCT-KD, medium-chain triglyceride KD; NA, not achieved; NAT, remote nonaccidental trauma resulting in epilepsy; NMDA, N-methyl D-aspartate receptor encephalitis; NORSE, new-onset refractory status epilepticus of unknown etiology; NR, not reported; PNA, pneumonia; POLG, mitochondrial polymerase γ related epilepsy; response %, proportion of patients who had resolution of SE; SE, status epilepticus; SNF, skilled nursing facility; STP, stiripentol; TBI, traumatic brain injury; TG, triglycerides; VRU, ventilatory rehabilitation unit.

[a]The patient received a parenteral 4:1 ketogenic diet treatment for 12 days, then switched to an enteral preparation administered via a gastrostomy tube.

[b]Includes one patient previously reported in Cervenka et al (2011)[89] which has been omitted from this table to avoid redundancy.

[c]The patient initially received a KD for 16 days without achieving ketosis so an SGLT2 inhibitor was added with consistent ketosis achieved 7 days later.

[d]Excludes one patient previously reported in Nam et al (2011).[67]

[e]Proportion of patients with ≥50% reduction in seizures.

[f]The patient initially received a KD but was switched to MCT-KD due to persistently elevated TGs after 2 weeks.