Clinical Neurophysiology Practice 2 (2017) 154–160

Contents lists available at ScienceDirect

Clinical Neurophysiology Practice

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

Review article

The role for ketogenic diets in epilepsy and status epilepticus in adults

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ARTICLE INFO

Article history:
Received 24 January 2017
Received in revised form 19 May 2017
Accepted 2 June 2017
Available online 1 July 2017

Keywords:
Ketogenic diet
Modified Atkins diet
Epilepsy
Drug-resistant epilepsy
Refractory status epilepticus

ABSTRACT

Ketogenic diet (KD) therapies are high fat, low carbohydrate diets designed to mimic a fasting state. Although studies demonstrate KD's success in reducing seizures stretching back nearly a century, the last 25 years have seen a resurgence in diet therapy for the management of drug-resistant epilepsy in children as well as adults. With ≥50% seizure reduction efficacy rates in adults of 22–55% for the classic KD and 12–67% for the modified Atkins diet, diet therapy may be in many instances comparable to a trial of an additional anti-epileptic medication and potentially with fewer side effects and other health benefits. Moreover, ketogenic diets offer promising new adjunctive strategies for the treatment of acute status epilepticus in the intensive care setting. Here, we review the efficacy and utility of ketogenic diets for the management of chronic epilepsy and refractory status epilepticus in adults and offer practical guidelines for diet implementation and maintenance.

Contents

1. Introduction of ketogenic diets

Since as early as 400BC, diet therapy has been described in the treatment of epilepsy with Hippocrates reporting the belief by contemporaries that certain foods (particular types of fish, fowl, goat, etc.) could exacerbate or cause seizures (Hippocrates., 400BC). Moreover, reference is made in the bible of a patient with epilepsy being cured through "prayer and fasting" (The Bible. Mark 9:14–29, 1982). Despite early reports of seizure reduction and improvements in cognition in adolescents and adults treated with high-fat, carbohydrate limited diets in the 1920s, interest in diet therapy waned following the introduction of anti-epileptic drugs until the 1990s when research studies and clinical trials in children demonstrated its efficacy in drug-resistant patients and particular pediatric epilepsy syndromes (Bastible, 1931; Barborka, 1930, 1928; Martin et al., 2016). There has subsequently been increasing interest worldwide in the use of ketogenic diets to manage drug-resistant epilepsy in adults as approximately 19.5 million people with epilepsy have seizures uncontrolled by medications (Moshé et al., 2015). Moreover, patients with seizures resistant to two or more anti-epileptic drugs have a less than 5% chance of seizure-freedom with additional drugs added and many patients may not be surgical candidates due to a generalized epilepsy, multifocal nature, or nonresectable location of ictal onset (Brodie et al., 2012; Kwan and Brodie, 2000). Thus, there remains a significant

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http://dx.doi.org/10.1016/j.cnp.2017.06.001
2467-981X/

demand for additional effective therapeutic options that the ketogenic diet can supply.

The classic ketogenic diet (KD) is a high fat, low carbohydrate diet that induces ketone body production through fat metabolism with the goal of mimicking a fasting state in the body's tissues, shifting the predominant caloric source from carbohydrate to fat (Cervenka and Kossoff, 2013; McNally and Hartman, 2012). It is typically composed of a 4:1 ratio of fat (in grams) to protein plus carbohydrates (in grams). It is possible to use lower ratios of 3:1 or 2:1 (referred to as a modified ketogenic diet) depending on age of the patient, individual tolerability, levels of ketosis and protein requirements (Zupec-Kania and Spellman, 1998). Ketosis, urinary or serum, is used as a marker of early compliance following diet initiation but levels of ketosis are not necessarily predictive of seizure improvement (Klein et al., 2014; Payne et al., 2011). Since the early 2000s, the repertoire of ketogenic diet therapies has expanded to include more 'relaxed' variant forms, including the modified Atkins diet (MAD), the low glycemic index treatment (LGIT), or the ketogenic diet combined with medium chain triglyceride oil (MCT), aiming to provide increased flexibility and palatability. The MAD, which was first introduced in 2003, is typically composed of a net 10–20 g/day carbohydrate limit which is equivalent to a ratio of 1–2:1 of fat to protein plus carbohydrates. It allows users more flexibility and does not require the weighing of food portions nor an initial hospital stay for implementation (Cervenka and Kossoff, 2013; Schoeler and Cross, 2016). The LGIT recommends 40–60 g daily of carbohydrates with glycemic indices <50 and approximately 60% of dietary energy derived from fat and 20–30% from protein (Muzykewicz et al., 2009). The MCT variant ketogenic diet uses medium-chain fatty acids provided in oil form as a diet supplement. It provides an option for individuals with carnitine deficiency, as carnitine is required for processing the long-chain fatty acids of the classic KD, and allows for greater carbohydrate and protein intake than even a lower-ratio classic KD (Neal and Cross, 2010). While the classic KD is principally used in children, it is also used in adults, particularly those who are tube fed. Similarly, the LGIT is typically used in children but can also be used in adults (Coppola et al., 2011; Pfeifer and Thiele, 2005). MCT supplements in combination with other diets and the MAD are used in both pediatric and adult populations but often with a lower net carbohydrate limit in children (Kossoff et al., 2013a; Lambrechts et al., 2012; Smith et al., 2011; Trauner, 1985).

2. Efficacy and indications in adults

The increasing demand for KD access in adult populations typically arises from two sources – children and adolescents already on KD therapy and patients with adult-onset epilepsy or epilepsy continuing into adulthood with no prior diet treatments either refractory to medications or wishing to avoid or limit anti-epileptic drugs due to side effect burden. Many children become seizure free on ketogenic diets and successfully wean off the diet within 2 years according to consensus guidelines (Kossoff et al., 2009). However, there is a risk of seizure recurrence with change to a less restrictive diet and some children treated with the ketogenic diet, particularly those with specific genetic, metabolic (such as glucose transporter type 1 deficiency syndrome) or mitochondrial conditions, require transition to long-term adult epilepsy care as they age past 18 (Kossoff et al., 2014, 2013b). Furthermore, adult patients with chronic epilepsy refractory to medications, adults with newly diagnosed epilepsy seeking to avoid anti-epileptic drugs, and those requiring lifelong seizure treatment are motivated to achieve seizure control for independence in activities in daily living, work, and driving. Thus, evidence supporting diet efficacy in adults is needed.

2.1. Management of chronic epilepsy

The efficacy of diet therapy is commonly classified in terms of seizure frequency with patients achieving ≥50% reduction in seizure frequency considered responders. A 2011 review of dietary treatments in adolescents (age 12–18 years) and adults (age > 18 - years) pooled data from seven studies of the classic KD to show that 49% of 206 patients had ≥50% seizure reduction and of these 13% were seizure-free (Payne et al., 2011). A more recent 2015 meta-analysis reviewed ketogenic dietary treatments in adults (age ≥ 18 years) from 12 studies of the classic KD (n = 168 patients), the MAD (n = 87 patients), and the classic KD in combination with a medium-chain triglycerides diet (n = 15 patients) (Ye et al., 2015). The efficacy rates of KD in adult intractable epilepsy ranged from 13–70% with a combined efficacy rate of 52% for the classic KD and 34% for the MAD. The number of adherers to diet therapy was reported in 11 of the studies with a combined compliance rate of 38% for the classic KD and 56% for the MAD (Ye et al., 2015). A more recent study of the classic KD noted 39% had a ≥50% seizure reduction (9 out of 23 patients ≥ 16 years of age) and 8% had a ≥90% seizure reduction (2 out of 23 adult patients) while a MAD study noted 31% had a ≥50% seizure reduction (4 out of 13 patients ≥ 16 years of age, using intention to treat analysis) (Kverneland et al., 2015; Schoeler et al., 2014). In the largest observational study published to date of 101 adult patients (age ≥ 18 - years) naïve to diet therapy who subsequently started the MAD, 39% had ≥50% seizure reduction and 22% became seizure free (Cervenka et al., 2016a). Thus, as summarized in Table 1, the classic KD reduces seizures by ≥50% in 22–70% of patients and ≥90% in up to 52% of patients and the MAD has a similar variability in published response rates, ranging from 12 to 67% with ≥50% seizure reduction and up to 67% of patients with ≥90% seizure reduction (Cervenka et al., 2016a; Johnson and Cervenka, 2017; Kverneland et al., 2015).

There is growing evidence of increased diet efficacy in certain epilepsy or seizure types. The ketogenic diet is the standard treatment for glucose transporter type 1 (GLUT1) deficiency, a rare genetic condition caused by impaired glucose transport into the brain and associated with an abnormality in the gene SLC2A1 (De Vivo et al., 1991). Studies have shown up to 90% of patients with seizure freedom on the ketogenic diet or modified Atkins diet, including adults (Cervenka et al., 2017a; Ramm-Pettersen et al., 2013). Similarly, for patients with pyruvate dehydrogenase deficiency, where the diet overcomes the deficiencies in the catalytic component of the mitochondrial enzyme pyruvate dehydrogenase complex by providing an alternative source of acetyl coenzyme A, the ketogenic diet is considered first-line therapy and should be implemented as soon as the patient is identified (Kass et al., 2016; Klepper and Leiendecker, 2007; Pong et al., 2012). There is also general agreement that patients with infantile spasms, Lennox-Gaustat syndrome, Dravet syndrome, Angelman syndrome (particularly with the LGIT) and myoclonic-astatic epilepsy benefit from a trial of diet therapy once there epilepsy has become refractory to medication (Nangia et al., 2012; Thibert et al., 2012). While there is a paucity of scientific evidence supporting efficacy of diet treatment as first-line therapy for these epilepsy syndromes given their relative rarity (Cervenka et al., 2017a; Rubenstein et al., 2005), there is evidence of particular effectiveness suggesting it may be appropriate to introduce the diet early (Barañano and Hartman, 2008; Bergin, 2017; Lee and Kossoff, 2011). In addition, high response rates and seizure freedom has been observed in adolescents and adults with juvenile myoclonic epilepsy with 2/3 of adults showing ≥50% seizure reduction and 1/6 adults seizure free in two separate small case series (Kossoff et al., 2013c; Kverneland et al., 2015). Similarly, a trend for increased benefit of diet therapy

Table 1
Summary of published responder rates in studies of ketogenic diet treatment of epilepsy in adults (age ≥ 16 years).

Author (Year)	Subjects, n	Diet	Duration, mo	Compliant, n (%)	≥90% sz reduction	≥50% sz reduction
Sirven et al. (1999)	11	4:1 KD	8	7 (64%)	3/11 (27%)	6/11 (55%)
Mosek et al. (2009)	9	4:1 KD	3	2 (22%)	0/9 (0%)	2/9 (22%)
Klein et al. (2010)	12	3–4:1 KD	4	8 (67%)	2/12 (17%)	5/12 (42%)
Cervenka and Kossoff (2013)	27	KD[a]	2–118	9 (33%)	52%[b]	70%[b]
Nei et al. (2014)	28	4:1 KD	24	5 (18%)	1/28 (4%)	13/28 (46%)
Schoeler et al. (2014)	23	2–2.5:1 KD	12	9 (39%)	2/23 (8%)	9/23 (39%)
Lambrechts et al. (2012)	15	KD[a]/MCT	12	5 (33%)	0/15 (0%)	2/15 (13%)
Coppola et al. (2011)	6	LGIT	2	5 (83%)	0/6 (0%)	3/6 (50%)
Kossoff et al. (2003)	3	MAD	3	3 (100%)	1/3 (33%)	1/3 (33%)
Carrette et al. (2008)	8	MAD	6	3 (38%)	0/8 (0%)	1/8 (12%)
Kossoff et al. (2008)	30	MAD	6	14 (47%)	1/30 (3%)	10/30 (33%)
Smith et al. (2011)	18	MAD	12	14 (78%)	0/18 (0%)	3/18 (17%)
Cervenka et al. (2012)	22	MAD	3	14 (64%)	4/22 (18%)	6/22 (27%)
Kossoff et al. (2013a,b,c)	6	MAD	2	5 (83%)	2/6 (33%)	4/6 (67%)
Ramm-Pettersen et al. (2013)	3	MAD	12	3 (100%)	2/3 (67%)	2/3 (67%)
Kverneland et al. (2015)	13	MAD	3	6 (46%)	1/13 (8%)	4/13 (31%)
Cervenka et al. (2016a,b)	87[c]	MAD	12	33 (38%)	13/87 (15%)	29/87 (33%)

Abbreviations: KD = classic ketogenic diet; MCT = medium chain triglycerides; LGIT = low glycemic index treatment.
[a] KD ratio not reported.
[b] Efficacy rates were reported as percentages only.
[c] Of 106 study participants who met ILAE criteria for drug-resistant epilepsy and study inclusion criteria, 87 elected to begin MAD.

has been detected for patients with symptomatic generalized epilepsy compared to patients with focal epilepsies (Nei et al., 2014).

Several studies of adults receiving diet therapy have reported other benefits of dietary treatment beyond seizure control. These include improvements in arousal, mood, alertness, energy, and concentration (Carrette et al., 2008; Schoeler et al., 2014; Sirven et al., 1999). Furthermore, quality of life scores tend to increase rather than decrease with diet therapy (Lambrechts et al., 2012).

2.2. Management of refractory status epilepticus

First-line therapy for the treatment of status epilepticus (prolonged seizure lasting longer than 5 min or recurrent seizures without return to baseline between seizures) is with a high-dose benzodiazepine (Shorvon and Ferlisi, 2011). Status epilepticus that continues despite appropriate first- and second-line anti-epileptic drugs is classified as refractory status epilepticus (RSE). Current treatment algorithms utilize intravenous anesthetic agents for 24 h or more to suppress RSE if second and third-line drugs do not stop seizures. If status epilepticus continues or recurs 24 h or more after the initiation of treatment with anesthetic agents, patients are diagnosed with super-refractory status epilepticus (SRSE) (Hocker et al., 2013). As both RSE and SRSE carry high rates of morbidity and mortality (Shorvon and Ferlisi, 2012), ketogenic diet therapy offers a needed adjunct strategy for management of status epilepticus. It has the potential advantages of working quickly and synergistically with other concurrent treatments, is relatively easy to start, monitor, and maintain in the controlled intensive care unit setting with close follow up, and it does not contribute to hemodynamic instability seen with anesthetic agents

Table 2
Summary of published studies of ketogenic diet adjunctive treatment of refractory and super refractory status epilepticus in adults (age ≥ 18 years).

Author (Year)	Subjects, n	Diet	Time to Diet Start (Days)	Time to Ketosis (Days)	Time to SE Response (Days)	Outcome	Etiology	AE
Bodenant et al. (2008)	1	KD	31	NR	7	Death	Epileptic encephalopathy, PNA	0
Wusthoff et al. (2010)	2	KD	20, 101	8, 10	6, 11	Home by 1 year	Rasmussen encephalitis; Viral Encephalitis	2 acidosis[d]
Nam et al. (2011)	1	KD	15	NR	7	Functional Baseline	Encephalitis	0
Martikainen et al. (2012)	1	LGIT	4	NR	4	Home	POLG	0
Strzelczyk et al. (2013)	1	KD[a]	16	4	4[b]	Home	Lafora disease	0
Thakur et al. (2014)	10	KD	2–60 (median 21.5)	1–7	1–31 (median 3)	7 ARF, 1 SNF, 1 VRU, 1 Death	4 NORSE, 2NMDA, 1 LGI1, 1 Anoxia, 2 Focal[c]	1 acidosis, 2 ↑TG
Amer et al. (2015)	1	KD	21	NR	14	SNF	NMDA	NR
Cervenka et al. (2017a,b)	15	KD	2–21 (median 10)	0–16	0–10 (median 5)	1 Home, 8 ARF, 2 SNF, 4 Death	5 NORSE, 2LGS, 3 ICH, 2 Anoxia, 1GBM, 1 Encephalitis, 1 NAT	4 acidosis, 2 GI, 2 HLD, 2 hypoglycemia, 1 hyponatremia, 1 wt loss

Abbreviations: AE = Adverse events deemed related to KD use; ARF = acute rehabilitation facility; GBM = glioblastoma multiforma; GI = gastrointestinal side effects (including constipation); HLD = hyperlipidemia; ICH = intracranial hemorrhage; KD = classic ketogenic diet; LGI1 = leucine-rich, glioma-inactivated 1 encephalitis; LGIT = low glycemic index treatment; LGS = Lennox-Gastaut syndrome; NAT = remote non-accidental 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; SE = status epilepticus; SNF = skilled nursing facility; 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 gastrostomy tube.
[b] The exact time to status epilepticus resolution is not reported although evidence documenting EEG improvement after achieving ketosis is provided and stable ketosis was achieved after 4 days of KD therapy.
[c] One patient had cortical dysplasia and one patient had neurocysticercosis.
[d] Both patients received oral bicarbonate supplementation.

Table 3
Minimum standards and recommendations for initiation of the classic ketogenic diet and modified Atkins diet.

Evaluations	Baseline (pre-diet)	Follow-up (at clinic visits)
Nutrition/Monitoring		
Mandatory:	Basic nutrition counseling Height & weight, calculation of body mass index (BMI) Food allergies/intolerances, food availability/preference	BMI changes Seizure Frequency
Recommended:	Three-day food record/calorie count Pre-diet seizure frequency *Consider monitoring start and end date of menses*	Food records/compliance Side effects *Changes in menses*
Laboratory		
Mandatory:	Basic metabolic panel, liver function tests (if on hepatically metabolized anticonvulsants) Urine human chorionic gonadotropin (premenopausal women)	Basic metabolic panel, lipid profile, urinalysis Urine ketones (if patient not doing well and considering stopping diet)
Recommended:	Complete blood count, lipid profile, liver function tests, calcium, vitamin D level *Consider free carnitine, selenium, magnesium, phosphorus, anticonvulsant levels, urinalysis, and urine calcium and creatinine ratios*	Liver function tests, vitamin D level, complete blood count, calcium, free and total carnitine, urine ketones *Consider selenium, zinc, magnesium, phosphorus, and urine calcium and creatinine ratios (especially if not on citrate)*
Diagnostic		
Mandatory:	Metabolic testing in children to identify etiology, if suspected high risk based on history	None
Recommended:	EEG/Epilepsy Monitoring Unit evaluation (if diagnosis unclear, patient suspected to be an epilepsy surgery candidate)	Bone density scan (every 5 years, minimum) Renal ultrasound (if nephrolithiasis suspected) Carotid ultrasound (if prolonged fasting lipid elevation)

Recommendations adapted from the International League Against Epilepsy approved consensus statement reviewing minimum standards for ketogenic diet programs (Kossoff et al., 2015) and based on practices at the Johns Hopkins Adult Epilepsy Diet Center (Cervenka et al., 2016a,b).

used to treat RSE. Moreover, there may also be an additional neuroprotective benefit related to improved mitochondrial function from reduced mitochondrial production of reactive oxygen species in response to glutamate (Maalouf et al., 2009) and other potential mechanisms of action that are beyond the scope of this review.

Several case reports and case series demonstrate the successful use of ketogenic diet therapy for management of RSE and SRSE (reviewed in Table 2). The first report of ketogenic diet use for SRSE in an adult was published in France (Bodenant et al., 2008). Subsequently, a 4:1 ratio ketogenic diet was introduced to two adult SRSE patients at the University of Pennsylvania after 20 and 101 days of seizures and resulted in seizure cessation after 6 and 11 days respectively (Wusthoff et al., 2010). Similar cases of successful resolution of status epilepticus in adults within 2 weeks and 4 days, respectively, for the classic KD and LGIT have also been reported (Martikainen et al., 2012; Nam et al., 2011; Strzelczyk et al., 2013). A case series of 10 adults with SRSE of median duration 21.5 days treated with a ketogenic diet (9 with a 4:1 ratio KD 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) (Thakur et al., 2014). In the most recent and largest case series of 15 adult patients treated with 4:1 ratio ketogenic diet therapy (14 of whom completed therapy) after a median of 10 days of SRSE at 4 medical centers, 11 (79% of patients who completed KD therapy) achieved resolution of seizures in a median of 5 days (range 0–10 days) (Cervenka et al., 2017b).

3. Guidelines for implementation and maintenance

Diet treatment for patients with drug-resistant epilepsy has many advantages. Diet therapies can be rapidly initiated and beneficial effects can be seen almost immediately. They can be used safely and effectively for most types of epilepsy and in patients of all ages. In addition, diet treatments are available worldwide and can be successfully implemented internationally (Kossoff et al., 2015). A traditional ketogenic diet service is comprised of at least 1 physician knowledgeable about ketogenic diet therapy and a registered dietitian or nutritionist, but other potential team members include pharmacists, social workers, nurses, nurse practitioners, and psychologists. Before starting a ketogenic diet therapy in adults, most commonly the modified Atkins diet, baseline nutrition and laboratory evaluations are warranted (as highlighted in Table 3). At a minimum, these include basic nutrition counselling, height and weight measures, and an assessment of food availability, preferences, allergies and intolerances. Mandatory baseline laboratory testing includes a basic metabolic profile and urine pregnancy testing (in premenopausal women), while a fasting lipid profile, complete blood count, liver function test, and vitamin D level to exclude deficiency are strongly advised (Kossoff et al., 2015, 2009). Suggested, but not required, follow up testing includes urinalysis, urine calcium and creatinine and serum levels of free carnitine, zinc and selenium. Measurement of anti-epileptic drug levels is recommended although there are relatively few concerns for drug-diet interactions. Despite a theoretical higher risk of kidney stones when ketogenic diets are combined with zonisamide or topiramate as both ketogenic diets and carbonic anhydrate inhibitors have been independently associated with nephrolithiasis (Furth et al., 2000; Maalouf et al., 2011), increased risk in combination-therapy populations has not been demonstrated in pediatric studies (Kossoff et al., 2002). Lastly, a teaching session for patients, families, and caregivers focusing on principles of diet therapy, compliance measures (serum or urinary ketosis), recommended hydration and nutritional supplements, potential adverse effects, and sample food recipes/menus is strongly advised (Cervenka et al., 2016a; Kossoff et al., 2015; Schoeler and Cross, 2016).

Adults who begin MAD are typically instructed to restrict net carbohydrates to 20 grams per day (subtracting fiber) and to consume liberal fat intake until satiety is achieved. Adequate hydration is recommended and patients are started on supplementation with a daily multivitamin, calcium and vitamin D (low carbohydrate brand). Patients track seizure frequency, urine and/or serum ketones, and weights. Recommendations regarding goal ketone concentrations, type, and frequency of measurement vary between ketogenic diet centers. Some centers encourage women of child-bearing age to record the start and end of menses as menstrual cycles can change or cease on ketogenic diets (Sirven et al., 1999). Clinic visit follow-up while on diet therapy is initially

recommended at 3 and 6 months and then annually for the duration of therapy. Assessments at follow-up visits can include review of seizure frequency, food records/compliance, side effects; height and weight measurements; and annual serum comprehensive metabolic and fasting lipid profiles. Annual serum complete blood count and levels of anti-epileptic drugs, vitamin D, zinc, selenium, and free and total carnitine are often performed. Additional suggested diagnostic testing include a bone density scan every 5 years at minimum as well as renal ultrasound, electrocardiogram, and carotid ultrasound if warranted by clinical circumstances. When patients elect to stop MAD, a tapering schedule consisting of increasing carbohydrates by 5 grams every 3 days until reaching 85 grams per day and decreasing fat intake ad libitum has been recommended and patients can then subsequently resume their pre-MAD diet (Cervenka et al., 2016a).

Implementation of the ketogenic diet to treat refractory and super-refractory status epilepticus requires a trained multidisciplinary team for successful administration. A dietitian or nutritionist familiar with the ketogenic diet is a critical member of this team. In addition, the entire intensive care unit team (including the pharmacist) needs to be aware of the dietary treatment as well as basic management principles (e.g., minimizing carbohydrates in medications, parental and intravenous fluids) in order to avoid inadvertently bringing the patient out of ketosis. For adult patients treated with a medically-induced coma for over 24 h with persistent status epilepticus or return after attempt to wean one or more anesthetics, the initiation of KD therapy may be considered. Based on recent protocols establishing safety of KD in treating SRSE (Cervenka et al., 2017b; Thakur et al., 2014), 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, amylase, and lipase. For initiation, under nutrition consultation/dietitian guidance, an enteral formula with a 4:1 ratio ketogenic liquid formula at half estimated caloric needs is administered for the first 24 h and then advanced to full calories. Multivitamin, calcium, and vitamin D supplementation should be co-administered at diet onset if the ketogenic formula used is not nutritionally complete. During maintenance, point of care glucose is tested every 4 h to maintain serum glucose >50 mg/dL, urine ketones and serum β-hydroxybutyrate are measured every 12 h, and a comprehensive metabolic profile is measured every 48 h to maintain serum bicarbonate >18 mEq/L. Sedating medications are continued and titrated to maintain seizure suppression for 72 h and then an attempt to wean sedatives is made. If successful, ketogenic diet therapy is continued with consideration of transitioning to a 20 gram net carbohydrate limit modified Atkins diet if and when the patient is tolerating oral intake. Ketogenic diet therapy is deemed unsuccessful if no improvement is seen after 2 weeks and discontinued.

Patients are generally not deemed candidates for KD adjunctive therapy if they exhibit severe metabolic or hemodynamic instability, liver failure, inability to tolerate enteral feeds, acute pancreatitis or pregnancy as possible teratogenic effects of ketogenic diet therapy are largely unknown (Cervenka et al., 2017b; van der Louw et al., 2017). In addition, patients that received any propofol infusion within 24 h may not be candidates for KD therapy based on a prior report of fatal propofol infusion syndrome in a patient receiving concomitant therapy for RSE (Baumeister et al., 2004). The use of the ketogenic diet for status epilepticus as with epilepsy is also contraindicated in patients with rare metabolic disorders that include 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 (Kossoff et al., 2009). These diagnoses are typically made in early childhood and not a major consideration in adults presenting with new-onset epilepsy or status epilepticus.

4. Adverse effects, compliance, and appropriate management

As with any treatment for epilepsy, ketogenic diet treatment has potential adverse effects, most commonly gastrointestinal effects, weight loss, and a transient increase in lipids in adults. The gastrointestinal side effects that include constipation, diarrhea and occasional vomiting are typically mild, improve over time, and can be managed with the assistance of a dietitian or nutritionist. Smaller meals, increased fiber intake and increased sodium and fluid intake can often prevent or alleviate these complaints. Weight loss may be an intended positive effect in patients who are overweight, but for those who want to maintain or gain weight adjustments in caloric intake can be made. Increases in serum lipids have been shown to normalize with continued diet therapy (after 1 year) or return to normal after cessation of diet therapy (Cervenka et al., 2016b; Klein et al., 2010; Mosek et al., 2009). In addition, very low carbohydrate diets that induce ketosis have been shown to lead to reductions in serum triglycerides, low-density lipoprotein and total cholesterol and increased levels of high-density lipoprotein cholesterol in adults (Paoli et al., 2013; Sharman et al., 2002). Adults with persistent hyperlipidemia who are responding well to diet therapy may consider increasing fat sources of omega 3 or adhering to published Heart Healthy recommendations for the MAD (Cervenka et al., 2016b).

Other potential side effects can result from vitamin and mineral deficiencies secondary to restricting carbohydrates, including osteopenia and osteoporosis (Bergqvist et al., 2008; Cervenka and Kossoff, 2013; Mackay et al., 2005), although the precise mechanism remains unclear and possibly hormone-related (Zengin et al., 2015). The standard practice of supplementing a recommended daily allowance of multivitamin and mineral supplements can prevent such deficiencies. Although side effects of the diet are often perceived to be a limiting factor for adult patients, a study of the classic KD in 23 adults showed that adverse events did not lead to discontinuation of the diet in any patient (Schoeler et al., 2014). Thus, while the proportion of users who discontinue diet therapy due to adverse events or perceived restrictiveness is wide-ranging, the most common reason for discontinuation of treatment tends to be lack of effectiveness (Payne et al., 2011; Ye et al., 2015).

Diet adherence and compliance remain significant barriers to successful KD implementation and an adequate assessment of efficacy. A meta-analysis of 11 studies of ketogenic diets in adults reported a combined adherence rate of 45% for all types of ketogenic diets, 38% for the classic KD and 56% for the MAD (Ye et al., 2015). Similarly, a recent observational study of 139 adult patients treated with ketogenic diets, 48% (67 of 139) discontinued the diet (39%) or were lost after initial follow up (9%) with approximately half of patients citing difficulty with compliance or restrictiveness as the reason for stopping (Cervenka et al., 2016a). These are in line with previous reports of adult drop-out rates of 51% for the classic KD and 42% for MAD in prior reviews (Klein et al., 2014). Although the MAD tends to be better tolerated by adults than the classic KD due to less restrictiveness, particularly in regards to restriction of calories, protein and fluid intake (Kossoff et al., 2008), it still requires a commitment to reduce carbohydrate intake and a change in lifestyle on the part of the patient and possibly their family. Often the provision of food menus/ recipes and resources to patients and families at the initial teaching session and subsequent visits can be helpful in emphasizing variety of food choices rather than perceived restrictiveness. Additional methods to improve diet adherence and compliance, as well as access for patients who live distant from a ketogenic diet center, include scheduled telephone

calls or electronic communication with the supervising dietitian and use of electronic applications like SeizureTracker® or KetoDietCalculator™ to prevent drop out within the first 3 months of treatment (Cervenka et al., 2012).

5. Conclusions

Ketogenic diets offer an increasingly needed adjunct to anti-epileptic drugs for management of chronic epilepsy and refractory status epilepticus in adults. Studies support feasibility, tolerability, and efficacy of the classic ketogenic diet and its variants in adults, although randomized control trials are needed. Potential complications and side effects of diet therapy are often preventable and manageable, nevertheless strategies are needed to improve adherence.

Conflict of interest

The authors declare no conflicts of interest. Dr. Cervenka receives grants from Nutricia, Vitaflo, BrightFocus Foundation, and Army Research Laboratory as well as Honoraria from the American Epilepsy Society, New York University, The Neurology Center, and LivaNova.

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