Practice Paper of the Academy of Nutrition and Dietetics: Classic and Modified Ketogenic Diets for Treatment of Epilepsy

ABSTRACT

Ketogenic diet (KD) therapy is an established form of treatment for both pediatric and adult patients with intractable epilepsy. *Ketogenic diet* is a term that refers to any diet therapy in which dietary composition would be expected to result in a ketogenic state of human metabolism. While historically considered a last-resort therapy, classic KDs and their modified counterparts, including the modified Atkins diet and low glycemic index treatment, are gaining ground for use across the spectrum of seizure disorders. Registered dietitian nutritionists are often the first line and the most influential team members when it comes to treating those on KD therapy. This paper offers registered dietitian nutritionists insight into the history of KD therapy, an overview of the various diets, and a brief review of the literature with regard to efficacy; provides basic guidelines for practical implementation and coordination of care across multiple health care and community settings; and describes the role of registered dietitian nutritionists in achieving successful KD therapy.
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SINCE ANCIENT TIMES, PROlonged periods of fasting have been used to treat epilepsy.[1] The first modern reports using fasting in epilepsy were by the French physicians Guelpa and Marie in 1911[2] and by Dr. H. Rawle Geylin, an American endocrinologist at New York Presbyterian Hospital.[3] Researchers at the Harvard Medical School were the first to report improvements in seizure control after 2 to 3 days of fasting, proposing that a change in metabolism occurred in the absence of food, specifically carbohydrate, forcing the body to utilize fat for energy.[4]

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Two parties first conceptualized the modern-day ketogenic diet (KD) independently in 1921.[4] Woodyatt[5] of Rush Medical College in Chicago noted that the ketones acetone and β-hydroxybuteric acid were formed through starvation on a diet low in carbohydrate and high in fat. Dr R.M. Wilder of the Mayo Clinic, in Rochester, MN,[6,7] proposed that a special diet be utilized for the treatment of seizures in efforts to achieve ketosis without inducing malnutrition that occurs with prolonged starvation. This was the origin of the classic KD.[4]

Ketogenic diet is a term that refers to any diet therapy in which dietary composition would be expected to result in a ketogenic state of human metabolism. A KD is generally defined as a high-fat, low-carbohydrate, moderate protein diet that aims to force the body to breakdown fat instead of glucose, both which provide adenosine triphosphate synthesis, essentially mimicking the metabolic state of starvation or fasting. KDs do not actually induce starvation; instead, they are precisely calculated to maintain adequate nutrient intake to prevent the malnutrition associated with starvation, therefore, ensuring healthy growth and development.[8] Calculations for classic KDs to this day remain similar to those first proposed by the Mayo Clinic group[9]—approximately 1 g protein/kg of body weight, 10 to 15 g carbohydrate/day, and the remaining calories from fat.

Use of KDs was common practice in the treatment of epilepsy through the 1920s and 1930s until the discovery of phenytoin in 1938.[4] As pharmaceuticals grew in number, the KD fell out of favor due to the perceived complexity of adherence. Although there was brief interest in a version of the KD rich in medium-chain triglycerides (MCT) in the 1980s, this was short-lived due to the gastrointestinal side effects of a diet composed of 60% total calories from MCT oil.[10] In 1994, the KD therapy grew in popularity after a highly publicized story, and eventual movie titled *First Do No Harm*, about a boy who quickly became seizure-free on the KD.[4] The resurgence in use of the KD led to the development of less-restrictive versions of the classic KD intended to enhance compliance; these diets are known as the Modified Atkins Diet (MAD)[11,12] and the low glycemic index treatment (LGIT).[13]

OVERVIEW OF EPILEPSY

Epilepsy is a chronic neurologic disorder that causes seizures, or a disruption in the electrical communication of the brain.[14] While seizures are considered a

symptom, epilepsy has been defined as having two or more unprovoked seizures at least 24 hours apart.[15]

According to the Epilepsy Foundation, 65 million people have epilepsy worldwide,[14] of which one-third are considered to have uncontrolled seizures that are refractory (uncontrollable) to standard medical treatment.[14] Although the etiology is often unknown, possible causes outside of mitochondrial and genetic disorders include an insult to the brain, such as traumatic brain injury, central nervous system tumors, infections, and substance abuse.[14]

Determining the type, duration, and intensity of the seizures is important in the diagnosis and treatment of epilepsy. Classification can be complicated, although two broad categories exist—primary generalized seizures and partial seizures. Primary generalized seizures involve the entire brain, beginning with widespread abnormal electrical activity, and can be characterized as either tonic–clonic or absence seizures. During tonic–clonic (convulsive) seizures, consciousness is lost and involuntary movement occurs,[14] whereas during absence seizures, the individual may lose awareness and appear to be dazed.[14] Partial seizures involve only one area of the brain, with symptoms varying depending on the area affected. Partial seizures can be classified as either simple, where consciousness is maintained, or complex, where consciousness is lost, followed by a period of confusion. The type of seizure(s) and location of origin in the brain are often the main determinant of treatment.[14] While some seizures can be controlled by anti-epileptic drugs (AEDs), others are considered refractory, and may require treatment via alternative treatment modalities, including diet therapy, surgical resection, and vagal nerve stimulation.

OVERVIEW OF KD THERAPY

Potential Mechanisms of Action

Although mechanism(s) by which the KD impacts seizure control are not completely understood, results from rodent and human studies offer multiple hypotheses, which can be classified into two categories: 1) alterations in energy metabolism, including a decrease in glucose concentration with an increase in fatty acid oxidation and ketone production; and 2) alterations in neurotransmitter production, release and uptake.[16-18]

Alterations in Energy Metabolism. As dietary carbohydrates are reduced, blood glucose decreases and ketone levels rise. Figure 1 offers a visual depiction of differences in fuel sources between a typical Western diet and a KD. The KD reduces the supply of glucose, decreasing glycolysis and due to adequate energy intake by way of fat consumption, prevents gluconeogenesis, resulting in increased β-oxidation, and a rise in ketone bodies, which become the main energy source for neurons.[16] Decreased glycolysis alone has been found to play a role in seizure reduction, with increased seizure activity noted with reintroduction of carbohydrates and subsequent rise in glycolysis.[19]

As carbohydrate intake decreases and fat intake increases on a KD, blood glucose stabilizes, and ketone production from both endogenous and dietary sources rise, offering a steady fuel source for the neurons, decreasing the likelihood of disruptions in energy availability.[8,17,19] The liver produces three types of ketone bodies, including β-hydroxybutyrate (BOHB), which is measured in the serum; acetoacetate, measured in the urine; and acetone, measured on the breath.

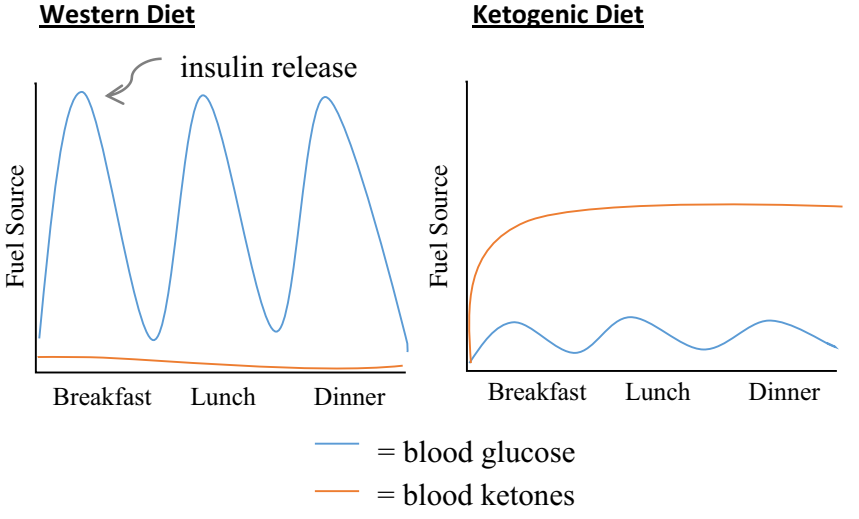

Figure 1. Variation in primary fuel source between a typical Western diet and a ketogenic diet. On a traditional Western diet, blood glucose rises after carbohydrate-rich meals (left), while on a ketogenic diet, carbohydrate intake is limited to only small quantities of those with low glycemic response, resulting in rises in serum ketone concentrations (right).

Alterations in Neurotransmitters. The second mechanism by which KDs may reduce seizure activity is through alterations in neurotransmitters, in manners similar to AEDs in many cases. Ketone bodies, specifically acetoacetate and BOHB,[20] have been found to inhibit γ-aminobutyric acid receptor-induced seizures.[21] KDs have been found to increase production and synaptic release of γ-aminobutyric acid, thereby reducing neuronal excitation and seizure activity by decreasing the conversion of glutamate to aspartate,[22,23] as well as potentially blocking neuronal uptake of glutamate through the presence of serum acetoacetate.[20] In addition, BOHB and acetoacetate may result in membrane hyperpolarization due to increases in adenosine triphosphate potassium channel activity, potentially reducing the release of neurotransmitters, and inhibition of action potentials.[22] Furthermore, ketones have been found to reduce reactive oxygen species and inflammation that results from seizure activity.[24]

Although no one mechanism has conclusively been deemed responsible for improved seizure control experienced with KD therapy, these mechanisms likely work in conjunction to control seizures in those who are affected by epilepsy.

Types of KDs

All KDs aim to reduce net carbohydrate intake and increase fat intake to

alter energy metabolism. Several variations of the KD have been found to be successful in the treatment of epilepsy; including the classic KD, MAD, MCT diet, and LGIT. Macronutrient composition of each diet in comparison to the 2015-2020 Dietary Guidelines for Americans can be found in Table 1,[25,26] along with a sample 1,700-kcal menu for the classic KD, MAD, and LGIT in Tables 2, 3, and 4.

Classic KD and MCT Diet. The classic KD is the most restrictive, requiring all foods and beverages be carefully calculated and precisely weighed on a gram scale.[8,27] The classic KD offers higher ketogenic potential and are prescribed as a ratio of grams of fat to combined grams of carbohydrate and protein, generally as 4:1 or 3:1, but also as low as 2:1, 1:1 ratios; while MAD, LGIT, and MCT, are typically ratios of 2:1 or 1:1. Ratios refer to grams of fat to combined grams of carbohydrate and protein (Table 1).

The MCT diet is more liberal in carbohydrates than the classic KD due to high intake of ketone-boosting MCT-rich fats, comprising up to 60% of total calories with a slightly more liberal carbohydrate content. Consumption of MCTs results in higher ketogenic potential due to ease of digestion and absorption, as they do not require bile salts for digestion; instead, MCTs are absorbed directly through the enterocyte, rapidly transported into portal circulation, and subsequently converted to ketones by the liver.[8] Use of the MCT diet is less common and sometimes limited by the unpleasant gastrointestinal side effects with consumption of high concentrations of MCT oil. Instead, smaller amounts of MCTs are incorporated into other versions of the KD to enhance ketosis. Due to limited use of the MCT diet, this paper will focus primarily on the classic KD, MAD, and LGIT.

MAD and LGIT. In the early 2000s, the MAD was first utilized at Johns Hopkins Hospital, and later the LGIT at Massachusetts General Hospital in efforts to ease implementation and adherence to KDs. These diets do not require gram scales; instead, portions are measured through standard household measurements. On the MAD, net daily carbohydrate intake is limited to 10 to 15 g for pediatric patients and 20 g among adolescents and adults,[11,12] while on the LGIT, daily carbohydrates are limited to 40 to 60 g/day from foods with a glycemic index <50 to prevent rapid changes in blood glucose and insulin levels.[13] Carbohydrates are encouraged to come from foods with high fiber contents, such as nonstarchy vegetables, nuts, and seeds. Although protein is not restricted on either version, intake above the needs of the average adult (0.8 to 1.2 g/kg actual or adjusted weight for an adult)[28] or above the dietary reference intake for age in pediatrics and adolescents may impact ability to maintain ketosis. Fat is encouraged on the MAD diet and the LGIT, ideally composing 60% to 70% of total calories.[8,27] Multivitamin and mineral supplementation is also recommended for patients on MAD and LGIT and will be discussed in greater detail later in the paper (Figure 2).

Efficacy

Impact on Seizure Frequency. While a comprehensive review is beyond the scope of this paper, results from two recent reports[29,30] offer insight into the benefits of KDs. Generally, efficacy is reported as a $\geq$50% improvement in seizure frequency, which is consistent with measures of efficacy among pharmaceutical outcome research for epilepsy. The KD and its variations may be effective for approximately half of those who trial it for drug-resistant epilepsy. A randomized clinical trial published in 2008[29] revealed that 44% of children had $\geq$50% improvement in seizure control. A systematic review of randomized controlled trials conducted among 427 children and adolescents indicate that when following a 4:1 classic KD, seizure freedom was observed in up to 55% of patients after 3 months of KD therapy and 85% reported seizure reduction.[30] Seizure freedom was achieved in 10% of children following an MAD, with 60% reporting a reduction in seizure activity. Outcomes for adults are more challenging to generalize due to limited publications; however, findings from a recent meta-analysis indicate that among 270 adults with intractable epilepsy, 52% of those following a

Table 1. Comparison of macronutrient composition and initiation requirements between various ketogenic diets and the 2015-2020 Dietary Guidelines for Americans[a]

Diet	Fat	Carbohydrate	Protein	Hospital admission
	←——— *range (%)* ———→			
2015-2020 Dietary Guidelines for Americans	20-35	45-65	10-35	No
Ketogenic diet ratio[b]				
4:1	90	2-4	6-8	Yes
3:1	85-90	2-5	8-12	Varies[c]
2:1	80-85	5-10	10-15	Varies[c]
Modified Atkins diet (1:1 ratio[b]**)**	60-65	5-10	25-35	No
Low glycemic index treatment (1:1 ratio[b]**)**	60-70	20-30	10-20	No
Medium-chain triglyceride diet (1:1 ratio[b]**)**	60-70	20-30	10	Yes

[a]Based on data from The Charlie Foundation for Ketogenic Therapies[25] and US Department of Health and Human Services.[26]
[b]Ratio refers to grams of calories from fat: carbohydrate+protein.
[c]Admission requirement may vary based on institution.

Table 2. Sample menu for the classic 3:1 ketogenic diet[a]

	Grams net carbohydrate	Fat (in grams)
Breakfast		
Egg Scramble (To prepare: Melt butter in frying pan; scramble all items together on medium heat.)		
71 g raw egg mixed well	0.51	6.75
17 g heavy cream	0.51	6.12
28 g butter	0.02	22.71
29 g feta cheese	1.2	6.17
21 g spinach	0.3	0.08
10 g mushrooms, chopped	0.23	0.02
10 g olive oil	0	22.71
Breakfast Subtotal:	2.76	64.56
Lunch		
Cobb Salad (To prepare: Toss all salad ingredients together in a bowl, top with olive oil and red wine vinegar.)		
72 g mixed greens	0.9	0.22
18 g avocado, sliced	0.33	2.77
68 g hard-boiled egg, chopped	0.76	7.21
14 g finely chopped bacon	0.42	6.3
15 g hard cheese shredded	0.27	4.55
31 g olive oil	0	31
15 g red wine vinegar	0	0
Lunch Subtotal:	2.68	52.05
Dinner		
Chicken and Zucchini "Pasta" (To prepare: Slice zucchini thinly into "noodles" and sauté in olive oil. Mix half the pesto into the zucchini and spread the other half on top of chicken. Basil Pesto recipe available at Ketodietcalculator.org)		
39 g baked chicken breast	0	1.4
80 g sliced or spiraled zucchini	1.69	0.26
28 g olive oil	0	28
32 g basil pesto	0.62	16.7
Dinner Subtotal:	2.76	46.36
Snacks		
Celery & Cream Cheese		
10 g stalk of celery, sliced	0.14	0
30 g full-fat cream cheese	1.1	10.3
Snacks Subtotal:	1.24	0
Daily Total:	**9.44**	**173.27**

[a]Approximate daily total: 1,700 kcal; 173.27 g fat : 9.44 g net carbohydrate + 45 g protein = 3:1 diet ratio. Nutrition information obtained from: www.ketodietcalulator.org.

classic KD and 34% on the MAD experienced ≥50% reduction in seizure frequency.[31] The authors concluded that diet compliance (defined as either self-reported positive urinary ketosis or by diet recall) was higher among those following MAD (56%) compared to classic KD (38%).[31] While efficacy rates vary, possibly due to fluctuations in compliance, populations that may experience higher success rates include patients with West syndrome and Lennox Gastaut syndrome.[28] Generally, classic KDs offer slightly higher efficacy, however, compliance is greater among modified KDs, such as MAD and LGIT, and therefore may be a better long-term therapy, particularly among those older than 2 years of age.

Limitations. Although current research regarding efficacy of the KD on seizure control among the pediatric population has been well established, results among use for seizure control in adults are limited by small sample sizes, lack of randomization, heterogeneity, high attrition rate, short study duration, and lack of description of dietary intake. Larger randomized controlled trials using various types of KDs are needed to better describe the benefits of KD therapy, particularly among adults with epilepsy. More research is needed to describe other potential benefits and side effects of KDs, including impact on seizure severity, quality of life, and long-term effects on health, as these diets become more common among the adult population. In addition, a detailed description of actual foods consumed by those on a KD (vs simple macronutrient breakdown) is needed to better understand how to achieve success and provide the most healthful therapy with the fewest complications.

KD Team Members

A well-trained, interdisciplinary team of health care practitioners is needed to initiate, manage, and best meet the complex and varying needs of patients on KD therapies. This team should include a neurologist and a nurse and registered dietitian nutritionist (RDN) both specializing in KDs, and should also include other clinical and community-based RDNs, epileptologists, nurses, nurse practitioners, pharmacists, social workers, case

Table 3. Sample menu for the modified Atkins diet[a]

	Grams net carbohydrate	Fat (in servings[b])
Breakfast		
Egg Scramble (To prepare: Melt butter in frying pan; scramble all items together on medium heat.)		
2 large eggs	1	1
2 Tbsp heavy cream	1/2	1
1 Tbsp butter	0	1
1/4 cup feta cheese	2	1/2
1/2 cup spinach	1/2	0
1/2 cup mushrooms, chopped	1	0
Breakfast Subtotal:	5	3 1/2
Lunch		
Cobb Salad (To prepare: Toss all salad ingredients together in a bowl, top with olive oil and red wine vinegar.)		
1 1/2 cups mixed greens	1/2	0
1/2 cup avocado, sliced	2	1
1 hard-boiled egg, sliced	1	1/2
1 Tbsp finely chopped bacon	0	1/2
1/4 cup blue cheese or cheddar cheese, shredded	1	1
2 Tbsp olive oil	0	2
1 Tbsp red wine vinegar	0	0
Lunch Subtotal:	4 1/2	5
Dinner		
Chicken and Zucchini "Pasta" (To prepare: Slice zucchini thinly into "noodles" and sauté in olive oil. Mix half the pesto into the zucchini and spread the other half on top of chicken.)		
1 medium baked chicken breast	0	0
1 cup sliced or spiraled zucchini	2 1/2	0
1 Tbsp olive oil	0	1
2 Tbsp pesto	1	1
Dinner Subtotal:	3 1/2	2
Snacks		
Celery & Cream Cheese		
1 stalk of celery, sliced	1	1
2 Tbsp full-fat cream cheese	2	0
Sugar-Free Gelatin, 1/2 cup	1/2	0
Snacks Subtotal:	3 1/2	1
Daily Total:	**16 1/2**	**11 1/2**

[a]Approximate daily total: 1,700 kcal, 16 1/2 g net carbohydrate, 75 g protein, 150 g fat (11 1/2 servings).
[b]1 serving=14 g of fat.

managers/discharge planners, and families. Case managers can be an important part of the diet therapy team when it comes to planning for patient discharge and establishing connections with durable medical equipment providers for patients receiving enteral or parenteral nutrition to ensure necessary product and equipment is provided. In some settings, the nutrition and dietetics technician, registered, under the supervision of the RDN, can function in support of the RDN by working as a liaison between foodservice and the RDN concerning the delivery of food and nutrition services to patients on KD therapy.

Successful KD implementation requires good interaction among the KD team, the patient, and his or her support systems. The importance of caregivers and family support is critical for success. They provide not only social support and encouragement, but often implement the KD, and therefore must have a firm grasp on not only the diet, but also how to identify and act quickly to minimize symptoms of intolerance and prevent a potential complication.

PRACTICAL IMPLEMENTATION

In 2009, the International Ketogenic Diet Study Group published guidelines for the clinical management of children receiving the KD[32]; however, these have not been updated and do not include specific recommendations for adults undergoing KD therapy. Offering more guidance is the newly revised resource by Kossoff and colleagues[28]: *The Ketogenic and Modified Atkins Diets: Treatments for Epilepsy and Other Disorders*, 6th edition. Much of the information in the following sections is based on recommendations from this resource from the Johns Hopkins group, as well as a manual published by The Charlie Foundation for Ketogenic Therapies, and was provided during ketogenic RDN training,[33] as well as the clinical experience of the authors.

Contraindications

It is crucial to assess patients for potential contraindications for KD therapy before initiation (Figure 3). Those with a history of certain metabolic disorders that limit fat metabolism or carnitine production should not be initiated on KD therapy.[32]

Table 4. Sample menu for the low glycemic index treatment[a]

	Grams net carbohydrate	Fat (in servings[b])
Breakfast		
Egg Scramble (To prepare: Melt butter in frying pan. Scramble all items together on medium heat.)		
2 large eggs	1	1
1 Tbsp heavy cream	1/2	1/2
1 Tbsp butter	0	1
1/4 cup feta cheese	2	1/2
1/2 cup spinach	1/2	0
1/2 cup mushrooms, chopped	1	0
1 medium grapefruit	18	0
Breakfast Subtotal:	23	3
Lunch		
Cobb Salad (To prepare: Toss all salad ingredients together in a bowl. Top with olive oil and red wine vinegar.)		
1 1/2 cups mixed greens	1/2	0
1/4 cup avocado, sliced	1	1/2
1 hard-boiled egg, sliced	1/2	1/2
1 Tbsp finely chopped bacon	0	1/2
1/4 cup blue cheese or cheddar cheese, shredded	1	1
1 Tbsp olive oil	0	1
1 Tbsp red wine vinegar	0	0
Lunch Subtotal:	3	3 1/2
Dinner		
Chicken and Zucchini "Pasta" (To prepare: Slice zucchini thinly into "noodles" and sauté in olive oil. Mix half the pesto into the zucchini and spread the other half on top of chicken.)		
1 medium baked chicken breast	0	0
1 cup sliced or spiraled zucchini	2 1/2	0
1 Tbsp olive oil	0	1
2 Tbsp pesto	1	1
Dinner Subtotal:	3 1/2	2
Snacks		
Celery & Cream Cheese		
3 small stalks of celery, sliced	1/2	0
2 Tbsp full-fat cream cheese	1	1
Yogurt & Strawberries		
8 oz plain/unsweetened Greek yogurt (4% milkfat)	8	1
1/2 cup strawberry halves (mix into yogurt)	5	0
Snacks Subtotal:	14 1/2	2
Daily Total:	**44**	**10 1/2**

[a]Approximate daily total: 1,700 kcal, 44 g net carbohydrate, 75 g protein, 140 g fat (10 1/2 servings).
[b]1 serving=14 g of fat.

Although not contraindications, additional factors to consider with suggested workup plans can be found in Figure 4. Choosing the right candidate and involving the patient and family in selecting the most appropriate diet is crucial when implementing KD therapy in order to optimize compliance and prevent unintended complications (Figure 5).

Initial Consultation

Initiation procedures based on diet type can be found in Figure 6. Before KD implementation, a consultation between the patient and KD team is needed.[34] During this consultation the team will conduct a full medical and nutritional assessment for appropriateness of KD therapy, as well as to determine the most appropriate diet. Social factors impacting diet are also considered at this time. While some patients arrive with a baseline understanding of KD therapy, the initial consult offers the KD team time to offer detailed KD education and guidelines, and establish both patient and team expectations. It is crucial to assess and confirm patient and/or caregiver comprehension of initiation protocols, required testing, and anticipated follow-up schedule to prevent confusion and complications.

Baseline Data: Anthropometric and Biochemical Values. It is imperative to obtain accurate baseline weight and height/length measurements to determine appropriate protein and energy requirements. These values are the basis on which individual diet regimens are calculated. Baseline biochemical values (Figure 6) are obtained to address abnormalities and screen for contraindications or areas of concern before KD therapy, as well as to be used as a comparison after diet implementation (Figure 3).[32]

Micronutrient Supplementation and Carbohydrate Composition of Medications. Supplementing with a daily multivitamin with minerals is recommended to ensure micronutrient needs are met.[28,32-35] Those on higher ratio (3:1 and 4:1) KDs require supplementation with additional micronutrients based on age-appropriate dietary reference intakes (Figure 2).[28] In addition, vitamin D supplementation is

Recommended supplements:

- Multivitamin with minerals and trace minerals
- Calcium with vitamin D

Optional supplements to consider based on specific patient needs:

- Selenium
- Magnesium
- Phosphorus
- Vitamin D
- Iron
- Probiotic
- Ecosapentanoic acid/ docosahexaenoic acid
- Medium chain triglyceride oil
- Laxatives
- Carnitine
- Citrates
- Table salt/light salt
- Digestive enzymes

Figure 2. Dietary supplementation for patients on ketogenic diets. Based on data from Kossoff and colleagues,[32] The Charlie Foundation for Ketogenic Therapies,[33] and Neal and colleagues.[35]

- Primary carnitine deficiency
- Carnitine palmitoyltransferase I or II deficiency
- Carnitine translocase deficiency
- β-oxidation defects
  - Medium-chain acyl dehydrogenase deficiency
  - Long-chain acyl dehydrogenase deficiency
  - Short-chain acyl dehydrogenase deficiency
  - Long-chain 3-hydroxyacyl-CoA deficiency
  - Medium-chain 3-hydroxyacyl-CoA deficiency
- Pyruvate carboxylase deficiency
- Porphyria

Figure 3. Absolute contraindications to using ketogenic diet therapies. Based on data from Kossoff and colleagues.[32]

recommended for those found to be deficient. Vitamin D deficiency is a potential side effect of certain AEDs.[36] Correction of the deficiency has been found to have an anticonvulsant effect.[37] All supplements should be in tablet or powder form when possible to minimize carbohydrate consumption. Ketogenic formulas are available for enterally fed individuals and are fortified with micronutrients, but may need additional supplementation to meet the dietary reference intakes for age.

All medications must be assessed for carbohydrate content before and during KD therapy, as many can add significant carbohydrates, particularly when taken multiple times daily.[38] In general, medications in liquid, syrup, and elixir formulations may contain carbohydrates in the form of sugars or sugar alcohols, and therefore, may disrupt ketosis. Pharmacists should be consulted for recommendations for low-carbohydrate formulations of medications when necessary.

Initiation of KD Therapy

KD therapy can be initiated in both the inpatient and outpatient environments as long as the patient or caregiver is prepared and well informed and there is a system in place for the patient and caregiver to access the KD team in the event of an adverse effect. All forms of KD therapy necessitate an intensive educational session. Educational formats vary by institutions, with some providing one-on-one sessions, and others employing a classroom-based environment with multiple patients.

Planned Inpatient Admissions. The rationale behind admission for diet initiation is to manage potential acute side effects and provide ample time for education over multiple days. Historically, the classic KD is initiated in the inpatient setting with a variable period of fasting; however, research indicates that fasting does not improve efficacy and may increase the risk of side effects, potentially increasing length of hospital stay.[39,40]

Initiation of classic and MCT KD therapy occurs by gradually titrating macronutrient composition during the course of 3 to 4 days.[28] The two initiation methods are as follows: 1) replace one traditional meal with a ketogenic meal on day 1, increasing to full KD therapy by day 3; or 2) increase the strength of the KD ratio daily as tolerated (1:1 ratio on day 1, then 2:1 ratio on day 2, and so forth, until goal ketosis is achieved). A slow KD introduction allows the gastrointestinal tract to acclimate to changes in macronutrient composition and induces ketosis gradually, which can be easier for the patient.

Diet initiation protocols for patients requiring enteral nutrition are similar to those who eat by mouth, providing a gradual increase in diet ratio. Multiple commercial ketogenic formulas are available, although at this time none are hypoallergenic. Blenderized formulas are an option for the caregiver with the time and ability to prepare recipes designed by a ketogenic RDN on a daily basis. Many hospitals are not equipped to offer blenderized formulas in the hospital setting, therefore, a backup recipe using commercially produced modular components may be necessary during a hospital admission.

During admission, it is important to monitor for and treat symptoms of acidosis, hypoglycemia, and excessive or persistent ketosis (Figure 2). If acidosis occurs, supplemental bicarbonate should be provided. Antiepileptic medications that promote acidosis should be evaluated and adjusted, if able, and/or the diet ratio lowered. Thresholds for treating metabolic acidosis vary by institution (serum bicarbonate <17 to 20 mEq/L), with acidosis generally treated with 2 to 3 mEq bicarbonate per kilogram of bodyweight.[32] Blood glucose should be monitored every 4 to 8 hours with the goal of >40 to 50 mg/dL (>2.2 to 2.8 mmol/L), depending on facility protocol. Glucose levels <40 to 50 mg/dL (<2.2 to 2.8 mmol/L) are treated with 15 to 30 mL juice and reassessed after 30 to 60 minutes.[33] If hypoglycemia persists, the team should consider lowering the KD ratio or increasing calories.[34]

Blood and urine ketone monitoring during hospital admission, as well in the home environment, varies by institution. Assessment of urinary ketones (acetoacetate) may be less accurate than serum BOHB levels.[41,42] Capillary BOHB has been found to have high sensitivity, specificity, and a positive predictive value for diabetic

Concern	Suggested Workup
Inability to maintain adequate nutrition or hydration • Failure to thrive • Dysphagia • Gastrointestinal issues (chronic diarrhea, vomiting, reflux) • Not able to meet fluid goals • Extreme picky eating/limited food acceptance	• Obtain gastrointestinal consult • Obtain swallow evaluation • Consider need for gastrostomy tube placement • Increase fat/kcal before initiation • Trial of 4:1 ketogenic formula • Provide recipes/foods to trial • Behavioral feeding consult
Concerning medical history • Extreme dyslipidemia • Cardiomyopathy • Renal disease/renal calculi • Liver disease • Baseline metabolic acidosis	• Obtain cardiology, nephrology, or hepatology consult for clearance • Adjust fluid minimums • Add citrate, consider bicitrate to alkalize urine, avoid/wean drugs like topiramate and zonisamide • Wean insulting medications if possible, increase fluid minimums, consider beginning with lower diet ratio
Social constraints • Access to food and kitchen • Caregiver support and compliance • Multiple caregivers/unstable home environment	• Connect family with social worker to discuss access to services, for example, but not limited to, durable medical equipment, Special Supplemental Program for Women, Infants, and Children, respite care, in home supportive services and/or formula company's assistance programs • Registered dietitian nutritionist can discuss meal/food options feasible for family

Figure 4. Considerations for determining appropriateness of initiation of ketogenic diet therapy and suggested further workup before diet initiation.

ketoacidosis, and negative predictive value for identifying diabetic ketoacidosis compared to urinary ketone testing,[42] although no studies have been published comparing BOHB to urine ketones among patients receiving ketogenic therapy. In addition, urine ketones levels may be influenced by hydration status,[43] as ketonuria has been found to have a small, negative association with urine osmolality, although this study was conducted in dogs. Generally, BOHB is assessed daily for level of ketosis during hospital encounters. Reference ranges for blood ketones (BOHB) can vary by laboratory, although the goal is positive ketosis.[28] Not all patients experience symptoms of excessive ketosis, and therefore do not need to be treated. Persistent hypoglycemia or symptomatic excessive ketosis despite multiple interventions may be indicative of an underlying metabolic condition and warrants further investigation.

Emergent Admissions. Most admissions for KD initiation are planned; however, there are occasions where emergent KD therapy is warranted. Although limited, the available research for use of KD therapy for status epilepticus is promising in both pediatric[44] and adult[45] populations. Status epilepticus is defined as continuous or near-continuous seizure activity without returning to baseline neurologic functioning.[28] KD therapy for status epilepticus appears to be most efficacious among those with underlying autoimmune and/or inflammatory conditions, such as infantile spasms (West syndrome) and febrile infection-related epilepsy syndrome.[46]

The goal of emergent KD therapy is to achieve ketosis as quickly as possible.[33] As all fluids, medications, and supplements are transitioned to carbohydrate-free products (if available), the patient is gradually transitioned to full calories provided by the KD during the course of 1 to 3 days, generally via enteral nutrition support,[28,45,46] achieving ketosis within 3 to 5 days. The KD should be provided at the highest ratio possible to achieve maximum ketogenic potential. Given the critical nature of status epilepticus and febrile infection-related epilepsy syndrome, minimum protein requirements may be temporarily sacrificed with the goal of achieving and maintaining ketosis. Levocarnitine may be initiated empirically for those receiving valproate or those found to have free carnitine deficiency, with dosing beginning at 50 mg/kg/day divided into three doses based on recommendations from The Charlie Foundation for Ketogenic Therapies manual.[33] Carnitine supplementation can improve ketosis and may need to be continued for the duration of KD therapy. A complete metabolic panel and serum BOHB are monitored daily until ketosis is established and levels stabilize.

Initiation in the Outpatient Environment. Less-restrictive versions of the KD, such as 2:1 or 1:1 classic KD, MAD, and LGIT can be initiated in the home environment, however, this requires a well-informed patient with a good support system. To

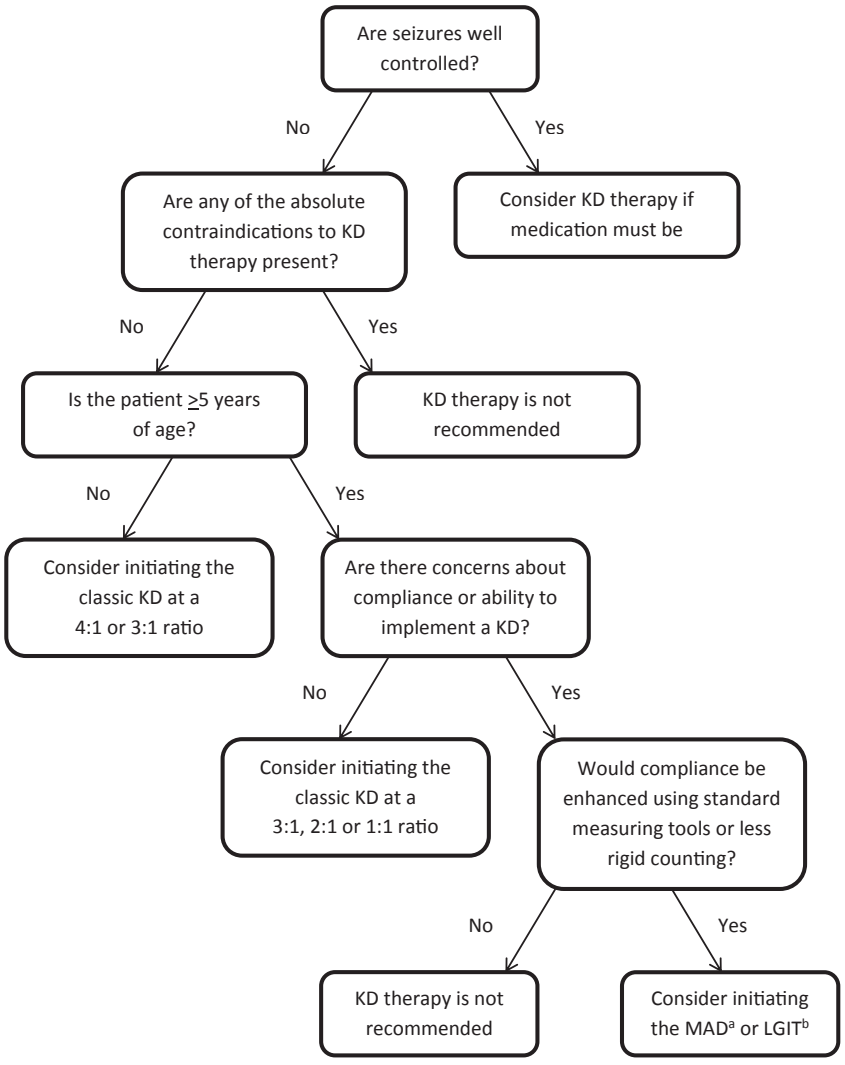

Figure 5. Ketogenic diet (KD) therapy initiation decision tree. [a]MAD=modified Atkins diet. [b]LGIT=low glycemic index treatment.

optimize success of home initiation, the patient, family, and/or caregivers must have a firm understanding of basic nutrition, an individualized diet prescription, as well as expectations and knowledge of how to manage potential complications, and have access to the KD team for any urgent issues.

Initiation of lower-ratio classic KD therapy in the outpatient home environment follows similar principals as their higher-ratio counterparts, and usually occurs during the course of several weeks. Success can be enhanced with close communication between the KD team and the patient or caregiver. For the classic KD, the diet is started at a 1:1 diet ratio with increases in the ratio weekly based on patient symptoms, tolerance to diet, seizure control, and laboratory values. The diet can be maintained at the ratio found to offer seizure control.

Education, instruction, and initiation for the MAD and LGIT are similar and conducted in the outpatient environment. Patients are educated on how to identify sources of protein, fat, and carbohydrate, how to count grams of net carbohydrate (total grams of carbohydrate minus grams of fiber) for those following MAD, and to identify foods with a low glycemic index (<50) for those following LGIT, in an effort to prevent fluctuations in blood glucose and insulin levels. Each patient may be given an individualized diet prescription that specifies net carbohydrate, protein, and fat recommendations. Patients are encouraged to start the MAD and LGIT therapies as tolerated over the course of a few days to weeks, depending on comfort level and tolerance.

Overall, monitoring in the home environment is less rigid than the inpatient setting. Some institutions require daily home blood glucose and blood ketone monitoring, while others simply monitor urine ketones daily, with the goal of moderate or large ketones. The gold standard for home ketone monitoring is blood ketone (BOHB) due to higher accuracy, which may be used to fine-tune the diet and achieve improved seizure control.[47] When BOHB measurements are not possible due to financial burden, urine ketones measured daily may be utilized. Correlation to seizure control has been observed between urine and blood (BOHB) ketones at low values, although poor correlation has been noted at higher values.[48] In addition, patients or caregivers are instructed to keep a log of daily dietary intake, weekly weight changes, and seizures, to help identify potential areas for improvement and minimize side effects.

Monitoring and Management. Monitoring and management strategies vary by institution, though they are generally more intense during the initial weeks and months of KD therapy. Those on a classic KD typically follow-up in an outpatient clinic with the KD team monthly for the first 3 months. Children under 1 year of age generally follow-up within 2 weeks, based on the clinical judgment of the KD team and individual institutional protocols.[32] Follow-up for the MAD and LGIT generally occurs 1 to 3 months after initiation. Patients are encouraged to contact the KD team by phone or e-mail if questions arise. Follow-up timing is similar across diet types after 3 months. Assuming no complications are experienced and the diet maintains efficacy, monitoring continues to occur every 3 to 6 months for the duration of therapy, but is adjusted based on patient need to enhance compliance and tolerance.[28]

At each monitoring visit, a complete nutrition assessment is conducted to assess nutritional adequacy, and biochemical values are obtained until stable or the diet is discontinued to assess for potential complications (Figure 6). Biochemical values are

Laboratory values	Pre-diet baseline	Daily during admission	1 and 3 mo post diet initiation	Every 3 mo until stable	Every 6 to 12 mo
Urine organic acids	X				
Plasma amino acids	X				
Complete metabolic panel	X	X	X	X	X
Complete blood count with platelets	X	X	X	X	X
Liver profile	X		X	X	X
Ionized calcium	X		X	X	X
Magnesium	X		X	X	X
Phosphate	X		X	X	X
Pre-albumin	X		X	X	X
Lipid panel (fasting)	X		X	X	X
Vitamin D-3	X			X	X
Free and total carnitine	X		X	X	X
β-hydroxybutyrate	X	X	X	X	X
Selenium	X			X	X
Zinc	X		X	X	X
Urinalysis	X		X	X	X
Urine calcium	X		X	X	X
Urine creatinine	X		X	X	X
Vitamins A, E, and B-12				X	X
Copper				X	X
Folate/ferritin				X	X

Figure 6. Standard laboratory assessment recommendations throughout various states of ketogenic diet therapy. Protocols may vary by institution, individual patient, and diet type. Based on data from The Charlie Foundation for Ketogenic Therapies.[33]

monitored regularly for abnormal values. One value of particular concern for many RDNs starting patients on KD therapy is the potential impact of diet therapy on lipid profiles. While fluctuations are likely to occur initially, these values generally remain similar to baseline, or actually may improve on KD therapy, specifically increases in high-density lipoprotein and reductions in triglyceride levels.[49-53] Serum low-density lipoprotein values occasionally rise with KD therapy,[54] though it is unclear whether it is the particle number or size that increases. Among healthy adults following low-carbohydrate diets for weight loss, low-density lipoprotein values increase due to an increase in particle size.[55] Larger, more buoyant low-density lipoprotein particles may be associated with a lower risk for development of atherosclerosis.[56] Among the general adult population, researchers report improvements in cardiovascular risk factors and management of type 2 diabetes when following low-carbohydrate diets[57-59]; however, it is unknown whether this remains true among those with epilepsy. Along with laboratory values, tolerance to diet, compliance, side effects, and weight trends are assessed. In the pediatric population, growth parameters are also monitored to assure that linear growth and weight gain increase proportionally over times with diet titrations as needed to ensure appropriate growth is maintained.[28]

Diet efficacy is assessed at each clinic visit, and is determined based on patient or family expectations of KD therapy, carefully weighing the benefits with the challenges of following the KD when determining continuation. While seizure freedom is the ultimate goal, patients may report other factors that impact choice to continue KD therapy, even if seizure frequency is not dramatically improved. These factors may include experiencing shorter, milder seizures, improved postictal states (period of altered level of consciousness after a seizure), increased mental clarity, or improvements in cognition or level of alertness. If the decision is made to discontinue the diet based on overall challenges or lack of desired benefits, the KD should be weaned gradually.

Fine-Tuning. Before initiation, patients and families are asked to give a 3-month commitment to KD therapy.

During this period (and often beyond), fine-tuning will likely be required to enhance the efficacy of the KD. Evidence correlating ketone level and diet efficacy is limited[47]; however, some patients benefit from higher levels of ketosis, or increased blood ketone (BOHB) levels, while others at milder or lower levels. Therefore, ratios may be adjusted to optimize ketone levels and potentially diet efficacy, if necessary. MCT oil may also be gradually incorporated and titrated to enhance ketosis. For those experiencing undesirable weight change or large fluctuations in blood glucose or ketones, a calorie adjustment may be beneficial.[34] Monitoring of free carnitine levels and initiating supplementation may increase KD efficacy (Figure 2).[35] For those on prolonged KD therapy, short periods of intermittent fasting may enhance ketosis and potentially increase efficacy.[60]

Adjusting for Tolerability and Enhancing Success. Mild side effects and tolerance concerns can occur during the first few days and weeks after KD initiation. Intolerance often presents as fatigue, headaches, nausea, constipation, hypoglycemia, or acidosis. If these symptoms occur, an oral citrate or sodium bicarbonate can be added to buffer acidosis, and/or the diet ratio can be decreased to improve tolerability and palatability. It is important to note that many oral citrate products contain significant amounts of carbohydrate, which must be calculated in the diet. The ketogenic and medical teams should work together to resolve the acidosis, potentially adjusting medication if necessary. Once tolerance has been established, the diet may be adjusted to increase ketogenic potential if needed for enhanced efficacy.

Close communication among the epilepsy nurse, ketogenic RDN, and patient or caregiver during the few weeks after initiation may enhance success, as compliance is the most important factor in successful KD implementation. Poor understanding and compliance will likely result in reduced efficacy and KD discontinuation. Offering encouragement via close monitoring and open lines of communication, as well as providing education materials, including sample meal plans and recommendations for eating outside of home and during social occasions, offer the patient support and encouragement during times when noncompliance is most likely, and may enhance KD success. In addition, because undesirable gastrointestinal side effects are another common reason for diet discontinuation, offering recommendations to prevent these effects, such as methods for ensuring adequate fiber and fluid intake, can enhance compliance and KD maintenance.

For those receiving enteral nutrition support, initial KD administration via continuous feedings may be better tolerated with a transition to bolus feeds once tolerance has been established. Standard ketogenic enteral formulas and modular, such as MCT oil and protein powders, may be necessary to enhance ketosis and meet protein needs. Soy or peptide-based formulas are available if food allergies or malabsorption are of concern and, as discussed previously, blenderized KD enteral regimens may be utilized if desired by the family; however, close monitoring and calculation by a ketogenic RDN is needed to maintain appropriate KD ratio and micronutrient goals.

Weaning and Discontinuation. Length of KD therapy often dictates length of time over which the KD is weaned, and guidelines for weaning may vary by patient and/or institution. KD therapy is usually implemented for a minimum of 3 to 6 months.[32,35] Patients generally follow KD therapy for several years. Many choose to continue the KD due to continued efficacy and/or improvements in other areas of life, such as mental clarity and alertness.[28] If compliance is not possible, the patient no longer wishes to continue KD therapy, or KD therapy is deemed ineffective early on, early discontinuation is possible.

Diet discontinuation should occur gradually and under continued supervision of the KD team to prevent the potential for rebound seizures.[32,35] For those on KD therapy for fewer than 3 months, carbohydrate content can be increased gradually by 1 to 5 g net carbohydrate per week, or by a 0.5 to 1.0 decrease in diet ratio per week until ketosis is lost.[28,33] For those on long-term therapy, this process should occur over the course of weeks to months. If seizures or other side effects occur with weaning, the KD should be resumed at the last point where it was effective. Once ketosis is lost and if seizures remain stable with discontinuation, patients are encouraged to continue to adhere to an overall healthy diet low in processed foods, specifically sugars.

ROLE OF THE RDN

Role of the Ketogenic RDN

Ketogenic RDNs require highly specialized training to ensure appropriate implementation and monitoring of KD therapy. RDNs with demonstrated and documented education and training with KD therapy are an integral part of the multidisciplinary team, and are vital in designing and maintaining a successful KD program. Ketogenic RDNs are involved in every aspect of therapy, from assessing appropriateness of KD therapy, education, providing recommendations for KD regimen, initiation, management of symptoms, to diet discontinuation. Ketogenic RDNs' primary role is to safely and effectively design a KD to optimize seizure control; this requires careful diet manipulation and planning, and can be demanding, as there are often many questions and additional communication with the patient and caregivers.

Appropriate staffing ratios. Staffing ratios vary widely. Unfortunately, no documented consensus as to the optimal ratio of patients to RDNs exists; therefore, it is difficult to provide recommendations for the number of full-time equivalents that would be necessary to maintain a successful KD program. With the rigorous demands of maintaining patients on KD therapy and potential for frequent, emergent hospital admissions, it is beneficial to have a minimum of two trained and competent ketogenic RDNs on staff, including a ketogenic RDN with pediatric experience if the program includes pediatric patients.

Models for RDN Reimbursement. Reimbursement and staffing models for RDNs specializing in KD therapy have yet to be standardized; therefore, models across other RDN specialties may serve as a reference.[61] Due to the need for highly specialized training, detailed diet education, close and

frequent monitoring, and risk for complications, ketogenic RDNs may spend more time with each patient, overall seeing fewer patients than standard RDNs. Inpatient models do not offer appropriate comparison, and most outpatient models may not appropriately categorize time involved to maintain a successful KD program. One major barrier for RDN reimbursement is the cost for care. Many clinics use a fee-for-service model in which insurance companies reimburse the clinic or clinician; however, this is only possible for an overall small number of diagnoses[62] for which KD therapy is not included. Even for reimbursable diagnoses, frequency of RDN visits is limited, regardless of patient need and clinical judgment. Reimbursement for KD therapy poses additional consideration due to the time necessary for intensive education, particularly with patients who require a hospital admission or have limited nutrition knowledge.[63] Ongoing and further advocacy is critical to expand RDN reimbursement for KD therapy.

Cost-Savings Analysis. The RDN is an integral part of the KD team in both the inpatient and outpatient settings and may not only improve clinical outcomes, but also increase overall cost savings.[64] While the cost benefit of RDN involvement on the KD team has not been established, use of KD therapy among children and adolescents with intractable epilepsy that experienced improved seizure control on KD therapy has resulted in an overall significant reduction in health care costs, including reduced medication costs when compared to pre-KD costs.[65-69] Further research is warranted to determine the cost benefits of KD therapy overall, specifically examining the cost savings when ketogenic RDNs are part of the treatment team.

Care Coordination: From Clinic to Community

Each patient should be provided with multiple customized letters to share with other members of their medical support team. These letters help ensure that KD guidelines are followed in a variety of settings, and can vary based on the audience. Important information to include is not limited to fasting protocols, blood glucose and ketone ranges, avoidance of carbohydrate-containing medications (if possible in nonemergent situations), meal and fluid schedules, and ingredients and equipment necessary for dietary management. For school-aged children or adolescents or adults residing in managed-care environments, coordination between ketogenic RDNs and the school or home environment is essential for KD success.

RDNs in the community may interact with patients following a KD and must be informed on the basics outlined in this review. The knowledge of KD therapy needed for RDNs in the community may include basic understanding of how to achieve and maintain ketosis, monitor for complications, and when and how to contact ketogenic experts for further guidance. This is particularly important in the hospital environment, as the primary KD treatment team can offer recommendations and adjustments, as well as offer basic education for those unfamiliar with KD therapy. If initiation of KD therapy is desired, it is crucial for the RDN and health care teams unfamiliar with KD therapy to reach out to organizations, such as The Charlie Foundation for Ketogenic Therapies or Matthew's Friends, and local experts for guidance to find appropriate recipes, baking mixes, equipment, menu ideas, and cooking demonstration (Figure 7). If outpatient KD therapy is desired, RDNs are responsible for receiving appropriate training and demonstrated, documented competency from these organizations, or referring the patient to RDNs with KD training.

- Academy of Nutrition and Dietetics Nutrition Care Manual: www.nutritioncaremanual.org
- Kossof EH, Turner Z, Doerrer S, Cervenka MC, Henry BJ. *The Ketogenic and Modified Atkins Diets: Treatment for Epilepsy and Other Disorders.* 6th ed. New York: demosHEALTH; 2016.
- The Charlie Foundation for Ketogenic Therapies: www.charliefoundation.org
- Matthew's Friends: www.matthewsfriends.org
- Carson Harris Foundation: www.carsonharrisfoundation.org
- Carley Eissman Foundation: www.carleyeissmanfoundation.com
- Keto Hope Foundation: www.ketohope.org
- KetoDietCalculator: https://ketodietcalculator.org
- Nutricia: www.myketocal.com
- Cambrooke Therapeutics: www.ketovie.com

Figure 7. Ketogenic references for registered dietitian nutritionists (RDNs). These resources were determined to provide quality ketogenic recommendations by RDNs practicing ketogenic diet therapy.

SUMMARY STATEMENT

RDNs play a unique and critical role in the assessment, initiation, management, and treatment of patients following KD therapy. Once an area of nutrition rarely utilized and considered unfeasible for most patients, particularly adults, use of KD therapy is rapidly expanding. It is the responsibility of all RDNs to be knowledgeable on the basics of KD therapy, their potential role in management, and how to locate experts in the field, particularly as this effective and novel treatment expands outside the realm of epilepsy, including possible management of malignant brain tumors and other various forms of cancer, autism, Parkinson's disease, Alzheimer's disease, traumatic brain injuries, mitochondrial disorders, and for weight management.

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