Dietary Treatment of Intractable Epilepsy

Mackenzie C. Cervenka, MD; Eric H. Kossoff, MD

ABSTRACT

Purpose of Review: Dietary therapies for seizure management date back further than pharmacologic interventions, but many neurologists are not familiar with these treatment options. This introduction to dietary therapies will discuss administration of ketogenic diets, comparisons between diet types, evidence-based efficacy of diet therapies in epilepsy treatment, and management of side effects. This review will provide the general neurologist with the skills to identify appropriate candidates for these treatments and to offer comprehensive ongoing care.

Recent Findings: In adults and children with medically resistant epilepsy, studies have consistently shown a greater than 50% reduction in seizure frequency in approximately one-half of patients within days to months after starting dietary therapy.

Summary: Dietary treatment options for epilepsy include the classic ketogenic diet, the medium-chain triglyceride diet, the modified Atkins diet, and the low glycemic index treatment. These were first used to control seizures in children with intractable epilepsy, but in recent years have also been demonstrated to be safe and effective in children and adults with a broad range of seizure types and are being used with increased frequency worldwide.
public on the use of the ketogenic diet for epilepsy.

Since this reintroduction of the ketogenic diet as a practical and tolerable option for seizure management in the mid-1990s, hundreds of studies have investigated its efficacy in epilepsy management. In an effort to provide a less restrictive alternative to the ketogenic diet, Kossoff and colleagues designed the modified Atkins diet in 2003 based on the observation that the Atkins diet produced urinary ketosis and provided benefit in seizure management, and Pfeifer and Thiele introduced the low glycemic index treatment in 2005. A consensus statement describing the use of these dietary therapies for epilepsy was published in Epilepsia in 2009. Dietary therapies have also become popular in the media, as featured in the film, “...First Do No Harm,” starring Meryl Streep.

OVERVIEW OF DIETARY THERAPIES FOR EPILEPSY

Dietary therapies are designed to mimic the starvation state but provide a long-term treatment plan for patients with intractable epilepsy. When deprived of glucose through restriction of carbohydrate intake, the human body begins metabolizing fat. In doing so, ketone bodies (acetoacetate, acetone, and β-hydroxybutyrate) are produced and can be measured in the serum and the urine. Diets that produce a state of ketosis are referred to as “ketogenic.” The classic ketogenic diet remains the most widely utilized dietary treatment and is effective in children with a variety of epilepsy syndromes. The classic ketogenic diet is traditionally started as a 3:1 or 4:1 ratio of fat to carbohydrates and protein in grams, of which 90% of the patient’s caloric intake is obtained from consumption of fat. Patients are typically admitted to the hospital for initiation of the ketogenic diet, which includes a 24-hour fast followed by gradual introduction of the diet over 2 days. Fluid and calories are strictly calculated, limited, and monitored, and all foods are weighed on a gram scale. Compliance and adequate fat intake with administration of the diet are monitored by measuring the degree of urinary ketosis, with the goal of achieving 80 mg/dL to 160 mg/dL or moderate to large urine ketones. The treating team typically includes a neurologist, a dietitian or nutritionist, a motivated patient, and the patient’s family.

Fats consumed in the classic ketogenic diet are derived mostly from long-chain fatty acids. Medium-chain triglycerides can be substituted with the potential advantages that these produce more ketones per kilocalorie of energy and are more readily absorbed. Therefore, medium-chain triglycerides used with the ketogenic diet may require reduced overall fat intake compared to a ketogenic diet using long-chain fatty acids to produce urinary ketosis. The traditional medium-chain triglyceride diet was initially designed to deliver 60% of energy from medium-chain triglycerides. Because this can produce problematic gastrointestinal side effects such as diarrhea, vomiting, and abdominal pain, a modified version was developed using 30% of energy from medium-chain triglycerides and 30% from long-chain fatty acids. However, ketosis may be more difficult to achieve using this regimen.

People using the Atkins diet for weight loss can go into a state of urinary ketosis during Phase 1 (or the induction phase) with a net carbohydrate limit of 20 g/d for 2 weeks. Net carbohydrates are calculated by subtracting the grams of dietary fiber from the total grams of carbohydrates in a food, because dietary fibers are not digested. With the modified Atkins diet, patients limit

KEY POINTS

- The traditional or classic ketogenic diet is a high-fat, carbohydrate-restricted diet with the primary goal of producing urinary ketosis and mimicking a starvation state without depriving the body of necessary calories to sustain growth and development.
- The classic ketogenic diet is traditionally started as a 3:1 or 4:1 ratio of fat to carbohydrates and protein in grams, of which 90% of the patient’s caloric intake is obtained from consumption of fat.
- Patients are typically admitted to the hospital for initiation of the ketogenic diet, which includes a 24-hour fast followed by gradual introduction of the diet over 2 days.
- Medium-chain triglycerides can be substituted for long-chain fatty acids with the potential advantages that they produce more ketones per kilocalorie of energy and are more readily absorbed. Therefore, medium-chain triglycerides used with the ketogenic diet may require reduced overall fat intake compared to a ketogenic diet using long-chain fatty acids to produce urinary ketosis.
their daily intake of net carbohydrates to 10 g/d to 20 g/d indefinitely. Rather than solely permit fat as the Atkins diet does, the modified Atkins diet requires increased fat intake, with the goal of achieving moderate to large urinary ketones. Fat to protein and carbohydrate ratios in these patients are closer to 1:1 than 3 or 4:1 as seen with the classic ketogenic diet. Unlike the ketogenic diet, calories and fluids are unrestricted and initiation does not require hospitalization or fasting (Table 11-1).

The low glycemic index treatment offers another, less restrictive alternative to the ketogenic diet by limiting consumption of foods with a high glycemic index.9

### TABLE 11-1 Comparison of Requirements for Common Dietary Therapies

<table>
<thead>
<tr>
<th>Requirements</th>
<th>Ketogenic Diet</th>
<th>Modified Atkins Diet and Low Glycemic Index Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calorie calculation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fluid calculation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>Yes or no, depending on practice in the institution</td>
<td>No</td>
</tr>
<tr>
<td>Weighing foods on a gram scale</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Fasting</td>
<td>Yes or no, depending on practice in the institution</td>
<td>No</td>
</tr>
</tbody>
</table>

Typically, over half of the calories from the “normal American diet” come from carbohydrates, followed by fat, low-carbohydrate diet is included (Table 11-2).

### TABLE 11-2 Sample Menu for High-Fat, Low-Carbohydrate Diets

- **Breakfast**
  - Coffee or tea with heavy whipping cream
  - Bacon and scrambled eggs
- **Lunch**
  - Water
  - Fried chicken wings (with pork-rind breading)
  - Celery sticks and blue cheese dressing
- **Snack**
  - Macadamia nuts
- **Dinner**
  - Diet soda
  - Broiled salmon
  - Steamed buttered cauliflower mashed potatoes
  - Sugar-free gelatin
and then protein. When comparing the composition of these dietary therapies to the normal American diet, all contain a higher percentage of fat and a lower percentage of carbohydrate calories, with the ketogenic diet having the highest and lowest, respectively (Table 11-3). The protein content is lower in the ketogenic diet and higher in the modified Atkins diet than in the normal American diet.

### Potential Mechanisms of Action

When the observation was first made that fasting or starvation resulted in seizure reduction, the reduction was thought to be related directly to being in a state of serum acidosis or ketosis. However, seizure reduction that results from starvation or treatment with ketogenic diets has not been shown to directly correlate with the degree of either acidosis or ketosis achieved. Recent research in animal models of epilepsy suggest that the mechanisms of action are much more complicated and may involve alteration in mitochondrial function, direct effects of ketone bodies on neuronal function and neurotransmitter release, antiepileptic effects of fatty acids, and/or glucose stabilization. Researchers have proposed that ketone bodies may increase membrane potential hyperpolarization; increase γ-aminobutyric acid (GABA) synthesis; or decrease release of glutamate, norepinephrine, or adenosine (Figure 11-1). Recent evidence also suggests a role of ketogenic diets in inhibition of the mammalian target of rapamycin (mTOR) pathway involved in the control of protein synthesis.

### Indications

Dietary therapies, most often the classic ketogenic diet, have been shown to be beneficial in treating a variety of epilepsy syndromes in children with frequent, medically resistant seizures. Dietary therapy has been reported as effective in the treatment of seizures associated with glucose transporter 1 deficiency, pyruvate dehydrogenase deficiency, infantile spasms (West syndrome), absence epilepsy, myoclonic astatic epilepsy (Doose syndrome), severe myoclonic epilepsy of infancy (Dravet syndrome), tuberous sclerosis complex, mitochondrial disorders, Lennox-Gastaut syndrome, Sturge-Weber syndrome, and Rett syndrome (Case 11-1,15-21). The ketogenic diet has been shown to work synergistically with the vagus nerve stimulator and with certain anticonvulsants such as zonisamide.23 Finally, several recent studies suggest efficacy of the ketogenic diet and modified Atkins diet in patients with medically or even surgically refractory status epilepticus (Case 11-2).24,25

Other populations in which dietary treatments may be considered are patients with gastrostomy tubes, because

### TABLE 11-3 Approximate Diet Composition by Percentage of Kilocalories

<table>
<thead>
<tr>
<th>Diet</th>
<th>Fat</th>
<th>Carbohydrates</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal diet</td>
<td>20–35%</td>
<td>50–70%</td>
<td>15–20%</td>
</tr>
<tr>
<td>Ketogenic diet (4:1)</td>
<td>90%</td>
<td>2–4%</td>
<td>6–8%</td>
</tr>
<tr>
<td>Modified Atkins diet</td>
<td>60–65%</td>
<td>5–10%</td>
<td>25–35%</td>
</tr>
<tr>
<td>Low glycemic index treatment</td>
<td>60–70%</td>
<td>20–30%</td>
<td>10–20%</td>
</tr>
</tbody>
</table>

KEY POINTS

- Seizure reduction that results from starvation or treatment with ketogenic diets has not been shown to directly correlate with the degree of either acidosis or ketosis achieved.
- Dietary therapies, most often the classic ketogenic diet, have been shown to be effective in treating a variety of epilepsy syndromes in children with frequent, medically resistant seizures.
liquid preparations of the ketogenic diet can be delivered as a replacement for their usual enteral nutrition with little lifestyle adjustment. Dietary treatments may also be of benefit in managing seizures in patients with comorbid conditions such as obesity and diabetes. In addition, dietary therapies are a consideration in developing countries where anticonvulsants are less available or more costly.26

**Outcomes**

Randomized controlled studies and meta-analyses have shown that approximately 50% of children with pharmacoresistant epilepsy have a greater than 50% reduction in seizures on the ketogenic diet.27 Y

In nearly all patients enrolled in studies of diet therapies, standard medical management has already failed with several anticonvulsants, resulting in the anticipated...
Case 11-1
A 5-month-old girl began having episodes of repetitive flexion of the torso and head with simultaneous elevation of the arms. Her parents took her to the emergency department, where the results of her basic laboratory studies, CT scan, and CSF studies were normal. An EEG revealed hypsarrhythmia and a child neurologist made the diagnosis of infantile spasms. The patient’s family was offered treatment options that included adrenocorticotropin hormone (ACTH), vigabatrin, and the ketogenic diet. They elected to start a trial of the ketogenic diet. The patient was admitted to the pediatric inpatient service and fasted for 24 hours, followed by initiation of a 4:1 ratio ketogenic formula over an additional 48 hours. The patient achieved urinary ketosis within 2 days, and her seizures stopped after 1 week and never returned. She demonstrated normal growth and development, and the ketogenic diet was stopped after 6 months; the seizures did not recur.

Comment. This case describes a patient with a severe childhood epilepsy syndrome that had a dramatic and long-lasting response to dietary treatment, used in a novel way as a first-line therapy.

Case 11-2
A 60-year-old man presented to the emergency department with recurrent right focal motor seizures and confusion. He was treated with IV benzodiazepines and a loading dose of fosphenytoin, but his seizures then evolved into nonconvulsive status epilepticus confirmed by EEG. The patient was transferred to the neurologic intensive care unit for more aggressive antiepileptic drug management and placed on continuous video-EEG monitoring. Trials of levetiracetam, valproic acid, phenobarbital, and lacosamide failed to control his seizures. The decision was made to treat with therapeutic burst suppression with IV pentobarbital. After 48 hours a pentobarbital taper was attempted, but seizures recurred. A gastric tube was placed for nutritional support, and the patient was started on a 4:1 ratio ketogenic diet. Within 10 days of starting the diet, he was producing large urinary ketones. A second attempt was made to taper pentobarbital at day 12, and epileptiform activity had resolved. The patient awakened and was ultimately transferred to rehabilitation. When he was able to take adequate oral nutrition, his diet was converted to the modified Atkins diet. He was discharged to home on a three-anticonvulsant regimen in combination with the modified Atkins diet, and over the next 6 months, anticonvulsants were tapered until he was on a single drug. He developed hyperlipidemia that reversed after his dietitian noted that he was eating several eggs daily and recommended reducing intake of eggs and fatty fish.

Comment. This case illustrates the successful use of dietary treatment in an adult with severely medically resistant status epilepticus with conversion from the ketogenic diet to the modified Atkins diet, simplification of the patient’s anticonvulsant regimen, and reversal of hyperlipidemia with appropriate dietary counseling.
success rate of adding more anticonvulsants of less than 15%. This makes the ketogenic diet a highly regarded treatment for intractable epilepsy.

Several important prospective studies have been published in recent years to demonstrate the effectiveness of dietary treatment. Neal and colleagues compared the classic ketogenic diet and the medium-chain triglyceride diet and showed that rates of greater than 50% seizure reduction were not significantly different at 3, 6, or 12 months; the authors concluded that these two treatments were of equal efficacy. A randomized crossover study compared the efficacy of a modified Atkins diet with a 10 g/d carbohydrate limit to a modified Atkins diet with a 20 g/d carbohydrate limit for 3 months in 20 children and found a significantly greater seizure reduction in the patients that followed the 10 g/d limit. After 3 months, participants switched to the opposite carbohydrate limit and both groups reported better tolerability with the 20 g/d limit compared to the 10 g/d limit.

Two studies have evaluated treatment with the ketogenic diet in comparison to a control group having no change in medical management. A blinded crossover study comparing efficacy of the ketogenic diet and glucose (control group) to the ketogenic diet and saccharine showed an overall reduction in seizure rate in the saccharine group, although these results were not statistically significant. Ketosis was not eliminated in all patients in the glucose group, which may have affected the results. Neal and colleagues performed a randomized controlled trial comparing treatment with the ketogenic diet to no change in seizure management in children who had failed to respond to two or more anticonvulsant drugs and found that after 3 months, 38% had a greater than 50% reduction in seizure frequency compared to 6% in the control group, which was a statistically significant difference.

Another study compared efficacy of the ketogenic diet to first-line treatment with adrenocorticotropic hormone (ACTH) in children with infantile spasms and found that the ketogenic diet was effective in stopping seizures in 62% as compared to 90% with ACTH. In those patients who did not respond to the ketogenic diet, switching to ACTH or topiramate produced almost immediate seizure cessation. Fewer side effects and relapses were seen with the ketogenic diet compared to ACTH; however, EEG normalization occurred more rapidly with ACTH compared to the ketogenic diet.

Efficacy rates of the ketogenic diet decrease slightly in the adolescent and adult populations. Decreased efficacy may be due to poorer compliance with strict calorie and carbohydrate limits and the added burden of weighing and measuring foods as part of daily living in adolescents and adults who are employed and who may themselves be care providers. These patients often have success with the modified Atkins diet or the low glycemic index treatment. Effectiveness of the modified Atkins diet is comparable to the ketogenic diet in children and adults. The overall percent of patients with a greater than 50% reduction in seizure frequency tends to be slightly smaller, but these differences are not statistically significant when comparing between studies. Dropout rates from dietary treatments vary tremendously between studies, ranging from 0% to 88% in one review. In that review, patients older than 12 tended to be less compliant and lack of efficacy was the most commonly cited reason for stopping. Patients also dropped out because of
side effects, restrictiveness, or (in some adolescents) peer pressure.

**Side Effects and Contraindications**

Side effects have been reported with the use of dietary therapies (Table 11-4), and are most often similar to those experienced with common medications. Constipation and nausea have been reported, but very rarely are fatalities linked to the use of dietary therapies. The state of ketosis caused by the diet results in metabolic acidosis as well, which can produce confusion and lethargy. Patients can have an increase in urinary uric acid and calcium, which may lead to nephrolithiasis.

Increased fat intake can lead to nausea, emesis, constipation, diarrhea, gastrolesophageal reflux, and in rare cases, acute pancreatitis, at times fatal. A diet high in saturated fats can cause hyperlipidemia, which is often reversible by substituting unsaturated fats (especially polyunsaturated fats) for saturated fats or lowering the ketogenic ratio. Other rarely reported side effects include cardiomyopathy, changes in basal ganglia of unclear significance on MRI, leukopenia, and increased susceptibility to infection due to decrease in immunoglobulin levels.

Carbohydrate restriction may be associated with vitamin deficiencies, particularly deficiencies in trace elements including zinc and selenium; carnitine deficiency; and hypoglycemia, hyponatremia, and hypomagnesemia. One rare complication caused by selenium deficiency is a prolonged QT interval that can lead to sudden cardiac death.

Thiamine deficiency can also occur and, in one report, was felt to be a cause of optic neuropathy in two patients on the ketogenic diet. Calcium and vitamin D deficiency can lead to osteopenia, osteoporosis, and bone fractures. As a result, all patients on any therapeutic ketogenic diet should receive daily multivitamin, mineral, and calcium supplements.

Ketogenic diets are contraindicated in patients with pancreatitis, hepatic failure, primary carnitine deficiency, carnitine palmitoyl transferase I and II deficiencies, carnitine translocase deficiency, beta-oxidation defects, pyruvate carboxylase deficiency, and porphyria.

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Prevention</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Hydration, high fiber</td>
<td>Increase fiber, polyethylene glycol</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>Unsaturated fats</td>
<td>Dietary counseling, statin</td>
</tr>
<tr>
<td>Acidosis/hyperketosis</td>
<td>Hydration, multiple small meals daily</td>
<td>Sip of juice, glucose</td>
</tr>
<tr>
<td>Kidney stones</td>
<td>Hydration, Urinary alkalinization (citric acid/sodium citrate, citric acid/potassium citrate)</td>
<td>Hydration, lithotripsy, stone removal</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Maintain baseline caloric intake</td>
<td>Increase fat/caloric intake</td>
</tr>
<tr>
<td>Hair loss</td>
<td>Multivitamin</td>
<td>Check zinc levels and replete if necessary</td>
</tr>
</tbody>
</table>

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**KEY POINT**

Ketogenic diets are contraindicated in patients with pancreatitis, hepatic failure, primary carnitine deficiency, carnitine palmitoyl transferase I and II deficiencies, carnitine translocase deficiency, beta-oxidation defects, pyruvate carboxylase deficiency, and porphyria.
therapy is being considered for treatment of refractory status epilepticus, the ketogenic diet is also contraindicated in patients who cannot tolerate enteral feeds (including those with ileus), in patients who are receiving a propofol infusion (to avoid fatal propofol infusion syndrome), and in patients who have metabolic, hemodynamic, or cardiorespiratory instability.

Monitoring and Management of Side Effects
Appropriate monitoring and follow-up with a neurologist and a dietitian or nutritionist is critical to the success of dietary therapies and to preventing, detecting, and treating side effects. This includes an initial evaluation with nutritional assessment to record height and weight and calculate body mass index; a medical evaluation with attention to comorbid medical conditions and potential contraindications; and a baseline laboratory assessment including complete metabolic panel, complete blood count with differential, fasting lipid panel, urine calcium and creatinine levels, and urine human chorionic gonadotropin (HCG) in women of childbearing age. Recommended follow-up assessments at 3 and 6 months include repeat fasting lipids and urine calcium and creatinine levels (to assess for risk of nephrolithiasis development).

Long-term studies that may be considered (but are not mandatory) when providing ongoing care for children or adults on diets for prolonged periods include a bone density scan every 5 years, annual serum zinc and selenium levels (especially in patients with reported hair loss), renal ultrasound if the patient reports symptoms concerning for nephrolithiasis, carotid Doppler studies if the patient experiences chronic hyperlipidemia, and in some cases an echocardiogram to screen for evidence of cardiomyopathy.

Managing patients on dietary therapies in the hospital or for unrelated medical conditions can at times be challenging because hidden carbohydrates can be given inadvertently—for instance by an emergency department physician administering IV fluids. Other medications such as over-the-counter cold medicines can also have carbohydrates and, when taken, can reverse ketosis and lead to breakthrough seizures. Pharmacists can be a valuable resource for identifying and avoiding these products.

TRENDS AND FUTURE DIRECTION
Animal studies are ongoing in an effort to understand the underlying mechanisms of the ketogenic diet and other dietary therapies. Some researchers posit that ketogenic states may be anti-inflammatory and neuroprotective as well as antiepileptic, suggesting additional therapeutic applications. Studies of diet therapies for neurologic conditions other than epilepsy are also being investigated, including ALS, Alzheimer disease, autism, Parkinson disease, stroke rehabilitation, and aging. More controversial uses of diet therapies that are being considered include diet therapies for monotherapy in patients with nonrefractory seizures who elect nonpharmacologic management, and for use in pregnancy. Another circumstance in which diet therapies may be of particular benefit is in developing countries with limited access to anticonvulsants. This introduces the challenge of treating patients in areas with a shortage of dietitian or neurologist support. Studies focusing on adults with epilepsy will continue to expand usage in this population.

CONCLUSION
Dietary treatments are an important and sometimes overlooked option for the management of patients with
medically resistant seizures and are particularly effective in certain childhood epilepsy syndromes. More patients are being started on dietary treatments for a variety of seizure types, and pediatric and adult neurologists must be able to identify and refer appropriate patients and detect and manage side effects.

**USEFUL WEBSITES**

Epilepsy.com.
www.epilepsy.com/Epilepsy/DietaryTherapies.

The Charlie Foundation.
www.charliefoundation.org.

Matthew’s Friends.
www.matthewsfriends.org.

The Carson Harris Foundation.
www.carsonharrisfoundation.org.

**REFERENCES**


