The Ketogenic Diet: Overcoming Challenges for Optimal Utilization in Epilepsy Treatment

Despite current logistical and clinical challenges, dietary therapy will play a significant role in epilepsy treatment for years to come.

By Amy Kao, MD

In the Hippocratic medical writings of ancient Greece and in biblical times, fasting was described as the treatment for epilepsy. The first report in modern medicine was in 1911, in which two physicians in Paris demonstrated decreased seizure severity in 20 patients during starvation. In 1921, a physician at the Mayo Clinic coined the term "ketogenic diet," proposing a diet consisting of excessive fat and sparse carbohydrates, which would produce ketones, just as starvation does. The ketogenic diet (KD) was extensively used as epilepsy treatment until diphenylhydantoin was discovered in 1938, and interest shifted for decades toward pharmaceuticals.

In the late 1980s, after learning about the KD, the family of a 20-month-old boy with refractory epilepsy named Charlie approached the Johns Hopkins Hospital requesting the treatment; it was effective for him. A subsequent *Dateline* episode and the 1997 film *Do No Harm*, starring Meryl Streep and directed by Charlie's father, helped publicize the KD. The family established the Charlie Foundation, a nonprofit organization that, to this day, provides information to parents and instructional materials to practitioners and dietitians.

Increased interest in the KD and other similar dietary treatments is evidenced by the rise in the number of associated scholarly articles. From 1930 to 1985, roughly zero to 10 articles were published about dietary therapies each year, after which a gradual increase has taken place. In 2016, the number of scholarly articles climbed to over 200 for the year, demonstrating a growing interest among the scientific community regarding various aspects, including outcomes, mechanisms underlying its benefit, and expanding indications. In addition to its role in epilepsy treatment, the KD has recently gained attention as a therapeutic intervention for a number of diverse conditions, including cancer, autism, Alzheimer's disease, Parkinson's disease, and traumatic brain injury.

The depth of research is, of course, greatest on the affliction for which its clinical benefit was first noted: epilepsy. In fact, several controlled trials have demonstrated that dietary therapies can decrease seizures in up to 40-50% of individuals with epilepsy. This article reviews both the challenges and advantages of the KD and explores how it may lead to more effective interventions for epilepsy.

The Ketogenic Diet: Basics and Challenges

When a "normal" diet is consumed, glucose is the sole source of energy for the brain. When carbohydrate consumption is limited, glucose supplies are low, so fat is used as the alternative energy source. Metabolically, when glucose is low, oxaloacetate is shunted from the citric acid cycle to gluconeogenesis, to produce and maintain glucose levels. This process decreases the efficiency of the citric acid cycle to metabolize the acetyl-coA

PRACTICAL POINTER

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generated from fatty acid metabolism; acetyl-coA is instead converted to ketone bodies. Ketone bodies can cross the blood brain barrier and are therefore used instead of glucose for energy.

The composition of the "classic" KD is calculated using a ratio of the weight of fat to the sum of the weight of protein and carbohydrates. Typical ratios are 3:1 or 4:1 (a standard North American diet is about 0.3:1). Calories are also measured to support growth and prevent excessive weight gain. Roughly 90% of calories are from fat in this diet. Historically, caloric and fluid restriction and an initial fasting period were features of the KD, but there are publications supporting efficacy and decreased side effects without these limitations. Even without these rigorous restrictions, initiation is typically performed inpatient to allow for monitoring and treatment of short-term complications, such as hypoglycemia and excessive acidosis, which can manifest as lethargy, irritability, vomiting, and dehydration.

Although the KD has demonstrated efficacy in appropriate patients, the unique nature of the modality results in logistical challenges. Chief among these hurdles are the personnel and time required for implementation and operation; many providers feel they do not have sufficient resources. The ketogenic diet as a treatment benefits from a multifaceted, multidisciplinary approach involving personnel with particular expertise in dietary therapies. Essential providers are the dietitian and physician (neurologist).

The role of the dietitian may include:

1. Reviewing dietary options to determine the most appropriate intervention based on estimated compliance and tolerability.
2. Formulating recipes in the prescribed ratio and suggesting particular foods.
3. Educating and supporting the patient and family regarding diet administration, with communications between visits.
4. Monitoring growth parameters and calculating caloric needs.

The role of the physician essentially involves weighing of benefits versus risks and monitoring medical safety, and may include:

1. Determining the appropriateness of a dietary therapy for the patient, based on diagnosis of refractory epilepsy or metabolic disease.
2. Defining goals of the dietary treatment.
3. Ensuring the lack of contraindication to dietary treatment.
4. Assessing risk for an adverse reaction and following pertinent monitoring labs.
5. Prescribing formula/supplies and providing documentation for insurance coverage.
6. Converting medication formulations to minimize carbohydrate intake.
7. Addressing complications.

Other potential beneficial team members include a nurse, a nurse practitioner, a social worker, and an authorization specialist.

In addition to being time-consuming for personnel, the KD can be overwhelming for patients and families. Once the ketogenic diet is started, the family must undergo a dramatic change in lifestyle (unless the patient is fed by gastrostomy tube), which requires significant organizational skills, time for food preparation, creativity, and a positive approach to optimize compliance and tolerability. Because dietary therapy programs require specialized expertise, before the diet is changed, patients may need to travel to treatment centers and experience long wait times for appointments and treatment initiation. These scenarios can also add stress and psychological burden.

The use of the KD is crucial for the treatment of certain metabolic conditions, including glucose transporter deficiency syndrome (in which glucose transport across the blood brain barrier is impaired) and pyruvate dehydrogenase deficiency (in which pyruvate cannot be metabolized into acetyl-coA). As more of these patients are recognized/diagnosed, more will require a dietary regimen for the long-term, potentially for the rest of their lives. Thus, it is important that we understand the level of risk for long-term side effects, including cardiovascular issues and osteoporosis. Research is ongoing to better elucidate these risks, but decision-making is still currently based on empiric treatment—weighing observed benefits against potential side effects. Close monitoring (up to every three to six months) for side effects is recommended, including measurements and laboratory testing for weight and height, hyperlipidemia, nutritional and electrolyte deficiencies, and kidney stones. Bone mineral density scan may be considered, particularly in patients who are high-risk (immobile, multiple antiseizure medications, history of fractures).

With such pronounced intensive needs in today's economically driven medical climate, optimizing care with KD can be achieved through a reorganization of systems to increase efficiency using available resources. Examples of useful efforts include allocating time for quality improvement endeavors to identify the numerous tasks throughout the process, clarify roles of personnel, and thereby avoid duplication or omission of tasks. Because dietary treatments require a high level of commitment for patients, educating the patient/family so they have a clear and realistic understanding and gauging their level of dedication and ability are important towards minimizing wasted efforts and setting the patient/family up for success. This assistance could be through assessments prior to meeting with the dietitian, either by a social worker or nurse/nurse practitioner, via mandatory review of an educational video, or through mandatory participation in a parent support group. A parent/patient support group, in which recipes, tips, and

Variations of the Ketogenic Diet

Other forms of the high-fat, low-carbohydrate diet have emerged and are sometimes used in epilepsy management. For instance, the **medium-chain triglyceride diet** uses medium chain triglyceride oil as a source of medium-chain fatty acids, which are more easily absorbed and delivered directly to the liver, thus generating ketones more efficiently, allowing greater protein and carbohydrate intake, but with risk of gastrointestinal side effects.

The **modified Atkins diet (MAD)** was developed at Johns Hopkins Hospital. The standard Atkins diet has a goal of weight loss and includes an induction phase in which there is limitation of carbohydrates to induce ketosis. In the MAD, carbohydrate restriction is continued and weight loss is not encouraged. The ratio of the MAD is 0.9:1. The protocol at Johns Hopkins limits initial carbohydrate intake to 10 to 15 grams per day for a month, with liberalization to 20 to 30 grams per day. The administration of the MAD is somewhat less laborious, requiring counting of carbohydrates but not inpatient initiation or weighing of foods. Urine ketones may be elevated to the "large" level but sometimes are lower than those generated by the KD. Evidence of longer-term adverse events with the MAD is limited, although in theory they would be less common.

The **low-glycemic-index treatment** is the least restrictive dietary therapy presently used in epilepsy care, but it also has the least amount of published research. It is initiated in the outpatient setting, without weighing of foods. The diet allows higher carbohydrate intake than the other two diets, but it limits the type of carbohydrates to those that result in lower postprandial blood sugar and insulin profiles. In the low-glycemic-index treatment, fat contributes 60% of calories, and carbohydrates are limited to 40 to 60 grams per day.

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emotional support are shared, can also improve adherence/tolerability and possibly decrease dietitian effort.

Technology is also helpful, via such applications as KetoDietCalculator, which hosts for dietitians and patients recipes, online resources, parent blogs, telemedicine visits, web-televised meetings, listservs, and social media pages. Thanks to the creativity propagated by motivated parents and technological advances, the KD today is more palatable, diverse, and easier to administer than the KD of even just 10 years ago.

Future Directions

The exact mechanisms by which dietary therapies treat seizures have not been precisely delineated. Much research, including animal model studies, has investigated this. The effects are likely multifactorial and include interactions between proposed mechanisms, such as direct anticonvulsant effect of ketones/free fatty acids, antioxidant/anti-inflammatory effects by decreasing reactive oxygen species, action on mitochondrial uncoupling proteins, increase of mitochondrial biogenesis, suppression of the mammalian target of rapamycin activity, decreased glutamate, and increased γ-aminobutyric acid. Identifying why KD works for some patients may allow us to offer other interventions and treatment options that target the same mechanism, for instance a pill form that would be easier for patients to take, or the addition of a medication to enhance effectiveness.

One aspect that has been explored recently is the role of fatty acids in the benefit of KD. Seizures impair the metabolism of glucose to pyruvate by glycolysis and the subsequent production of adenosine 5′-triphosphate by the citric acid cycle, and cause oxidative stress. Decanoic acid, which is a fatty acid given in the medium chain triglyceride diet (see sidebar), may have direct antiepileptic effects and inhibits excitatory α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, similar to the mechanism of action of perampanel (Fycompa, Eisai), an antiseizure medication approved in 2012. Decanoic acid has also been demonstrated to bind to the γ isoform of the peroxisome proliferator-activated receptor agonist (PPAR-γ), a nuclear receptor involved in mitochondrial biogenesis, and thus lead to increased mitochondrial numbers and antioxidant capacity. In addition, the administration of a peroxisome proliferator-activated receptor agonist, pioglitazone, with a 1:1 KD, synergistically decreases seizures.

These recent advances have serious potential to lead to new treatment options. Research toward mechanistic targets continues concurrently, as clinical centers aim to surmount the pragmatic and safety-related challenges of the KD. With these varied aspects being targeted, and the expanded interest for conditions beyond epilepsy, the next few decades may bring another new era for dietary therapies. ■

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