PRN OPINION PAPER

The Ketogenic Diet

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The ketogenic diet was designed in the 1920s to mimic the body's response to starvation. Starvation induces a ketotic state, shifting the body's metabolism from carbohydrate to fat utilization for fuel. Some patients with epilepsy who were in this ketotic state experienced a decrease in seizures. In its heyday, the diet was predominantly used to treat patients with intractable childhood epilepsy. The efficacy and tolerability of modern antiepileptic drugs (AEDs) led to decreased use of the ketogenic diet.

Recently, however, there has been a rebirth of popular interest in the ketogenic diet following the television news documentary *Dateline*, a movie made for television *First, Do No Harm*, and a published report on the diet's efficacy in 58 patients.[1] Its place in therapy is not well described, but it appears to be useful when traditional AEDs have failed or there are unacceptable side effects from AED therapy.

Pharmacists need to be aware of the ketogenic diet and recognize the importance of the carbohydrate content of additional medications the patient may be taking. Additionally, pharmacists need to educate patients and/or their caregivers on ketone monitoring.

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Background

When the body is deprived of glucose, ketone bodies, acetoacetic acid (AcAc) and β-hydroxybutyrate (BHB), are formed from the breakdown of fat and cross the blood-brain barrier where they can be used by the brain for energy.[2] The ketogenic diet's aim is to simulate the body's response to starvation by inducing production of these ketone bodies.[3, 4] This diet is high in fat and low in carbohydrates and protein, with each component of the diet being meticulously weighed in a specific ratio and proportion. Foods in this diet are considered either "ketogenic" (fat) or "antiketogenic" (carbohydrates and protein).[3, 4]

Accuracy and compliance with the diet are critical. It takes dedicated individuals to make the diet a successful seizure treatment. When patients are ill and either cannot ingest their diet properly or need to take additional medications (which generally contain carbohydrates), disruption of ketosis becomes more likely. It is therefore important for health care practitioners, patients, and family members to easily recognize the carbohydrate content of frequently used medications and other ingested products.

Pharmacists are the ideal source to supply this information and are essential to make the diet work with the least amount of effort.

Descriptions of the Ketogenic Diet

The modern form of the ketogenic diet was described by Wilder in 1921.[3–15] Wilder initially described a diet high in fat content (i.e., long-chain saturated fats) with a low percentage of both proteins and carbohydrates. This diet is

referred to as the "classic" (4:1 or 3:1) diet comprising four or three parts fat:one part nonfat (protein or carbohydrate) kilocalories. Wilder believed this would mimic the fasting state while providing the body with enough calories to maintain proper growth and function.[6]

Because the classic 4:1 diet was considered unpalatable and, hence, associated with poor compliance, Huttenlocher developed a medium-chain trigylceride (MCT) diet.[6, 16] The MCT diet is easier to prepare, is more ketogenic because the fats used (decanoic and octanoic acids) yield more ketones per calorie, allowing more carbohydrate and protein utility, and thus causes less elevation of serum cholesterol.

In addition to the classic 4:1 and MCT diet, a third diet—the modified MCT diet—was developed by the John Radcliffe Hospital in Oxford that incorporates both long- and medium-chain fatty acids.[6]

Proposed Mechanisms of Action

Numerous theories have been proposed on how the ketogenic diet works in both human[4, 9, 10, 13] and animal[15, 17, 18] studies. Several authors believe that the anticonvulsant effects of the ketogenic diet are related to the ketosis and production of AcAc and/or BHB.[3, 4, 9, 10, 13, 19] The protection against seizures by elevated blood levels of BHB and AcAc in animals also has been studied.[15, 20, 21]

The mechanisms of the ketogenic diets, however, are still unknown. It does appear that BHB and AcAc are involved in the efficacy of the ketogenic diet, but elevation of these substances may not be the only mechanism of action of the diet. More animal and human research is needed to completely determine the true mechanism or mechanisms of the ketogenic diet.

Efficacy

Ketogenic diets have been used to treat seizures that are both idiopathic and symptomatic. Patients with the following seizure types have been evaluated for efficacy of the diet: myoclonic, focal motor, atypical absence, generalized tonic, and tonic-clonic. All three of the diet formulations are equally efficacious.[3, 6, 8, 22] Overall efficacy ranges from 33–67%. Most of the studies that have been published use seizure frequency, intensity, and compliance as end points of the study.

It appears that children younger than 10 years old respond the best to the diet from a physiologic perspective.[3, 8, 13] These children tend to be more prone to ketosis than older children or adults. The brain's ability to extract ketone bodies and utilize them as an energy source decreases with age. This is because the relative fractional extraction of ketone bodies decreases with age.[23–25] Younger children are also more dependent on someone else preparing their diet than are older children or adults. Surprisingly, a majority of the children do not mind the taste of the high-fat diet, especially if they are involved in the selection of foods and their parents explain the importance of the special diet to them.

With regard to the above studies, it appears that sustained ketosis is an important factor in increasing the seizure threshold. The seizure protection afforded by the ketogenic diet may be reversed in as little as 1 hour of a patient receiving a glucose infusion.[13] This highlights the importance of strict adherence to the diet.

Adverse Effects

When the ketogenic diet is started and the patient is becoming ketotic (from starvation), a lethargic phase is usually seen. This is probably due to the sedative effects of the ketone bodies that Wilder described in 1921. In this initial phase, the patient is at risk for hypoglycemia and should be monitored frequently for its occurrence. Generally, these patients are hospitalized during this initial phase so that they can be closely monitored and intensive dietary education can be initiated with the caregiver. If the diet is not started in the hospital, it is expected that patients would routinely monitor their glucose concentrations while the diet is being started to protect against hypoglycemia.

The most common adverse effects encountered with ketogenic diets after the initial phase are gastrointestinal (GI) including nausea, vomiting, and abdominal cramping. These adverse effects are seen in approximately 50% of patients on the MCT diet because of its hyperosmolar concentration, and are somewhat less common with the classic diet. Excessive ketonemia also may produce GI side effects and should be ruled out. On a daily basis, urinary ketones should be monitored. Pharmacists are excellent resources for explaining how to monitor urinary ketones. A small amount of orange juice may be given for excessive nausea to lessen the degree of ketosis.[20] Medium-chain triglyceride oil is hyperosmolar, which can cause a large influx of fluid into the large intestines. When GI side effects are present

with the MCT diet, they can be eliminated by decreasing the amount of MCT oil in the diet and gradually titrating it back up slowly. It may also be helpful to have the patient sip the MCT drink throughout a meal to decrease abdominal pain. A few severely retarded children treated with the classic diet have developed dehydration and severe metabolic acidosis during illnesses, requiring hospitalization. When these children required intravenous rehydration, electrolyte solutions without glucose or lactate were given.[20]

Recently, carnitine deficiency has been reported in a small number of children receiving the ketogenic diet.[26] Baseline and periodic serum carnitine levels should be evaluated in patients receiving valproate, phenobarbital, phenytoin, or carbamazepine (which may also cause carnitine deficiency) who also are being treated with the ketogenic diet.[26–28] At this time, the significance of this interaction is unknown, and some clinicians contend that the only way to truly monitor carnitine stores is by muscle biopsy.

There are a few adverse effects that are seen uncommonly with ketogenic diets. Steatorrhea has occurred with the classic diet when a higher-than-recommended fat level was given. Optic neuropathy has occurred in patients who were not receiving vitamins (vitamin supplementation is discussed below).[29] Neutrophil impairment[7] and urolithiasis have also been reported. Appropriate monitoring for these adverse effects should be initiated.[3, 30]

Generally, growth has not been affected except in two infants under 1 year of age who had no increase in weight, length, or head circumference for 6 months.

Hyperlipidemia with significant elevations in serum cholesterol, triglycerides, and total lipids may occur.[20] A serum lipid panel should be obtained prior to diet initiation and periodically throughout the treatment.

Unfortunately the long-term effects of these diets have not been widely studied and published. One study examined adults who were treated with the classic diet in their childhood.[31] When blood cholesterol analyses were performed, these patients exhibited no abnormalities.[31]

Food-Drug Interactions

Acetazolamide should be used with caution in patients receiving the ketogenic diet because severe metabolic acidosis may occur, especially in younger children. If the patient is to remain on acetazolamide, it should be temporarily discontinued prior to diet initiation. The drug may then be restarted cautiously after metabolic adaptation has occurred.[20]

Phenobarbital serum levels may increase significantly in patients receiving the diet and may cause profound sedation.[32] This is related to the acidotic state induced by the ketogenic diet and the low pKa of phenobarbital, resulting in phenobarbital accumulation in the central nervous system.[28] When the diet is initiated, phenobarbital should be tapered, or the dosage decreased with serum levels monitored.

Valproate can interfere with ketone production, causing carnitine deficiency and a Reye's-like syndrome.[33] This syndrome can cause lethargy, nausea, vomiting, hepatic failure, and encephalopathy.[28, 33] Carnitine levels should be monitored at baseline and periodically if patients are receiving concomitant antiepileptic drugs, especially valproate, or show clinical evidence of carnitine deficiency.[28] L-Carnitine replacement may be warranted in patients with low carnitine levels, although the significance of carnitine depletion is unknown.

To maintain ketosis, it is essential that all carbohydrates in the diet are included in the dietary calculations. Even a small amount of additional carbohydrate that is not calculated into patients' daily diets may be enough to cause a recurrence of seizure activity by pushing them out of ketosis. Should this occur, the entire process of restarting the diet must take place. Many medications that children take are in liquid form, which often have carbohydrate-syrup bases. Capsules and tablets also contain carbohydrates as inert substances, but, in general, they are significantly lower in carbohydrate content.

Ketogenic diets require patients to take vitamin supplemention. Patients and their families need to know which vitamin supplements they can take safely (e.g., no carbohydrate content or the amount of carbohydrate to be calculated into their daily needs). Because this information is not easy to obtain and generally requires contact with the drug manufacturer, pharmacists are instrumental in retrieving this information. Sometimes the manufacturer's list of inert contents is not current and requires a phone call to the pharmaceutical company. A comprehensive list of frequently used medications and their carbohydrate content was published recently.[28]

Dietary Inadequacies of the Ketogenic Diet

The classic ketogenic diet is insufficient in several

vitamins and minerals: B complex, vitamins C and D, folate, iron, calcium, magnesium, and zinc. The MCT diet is insufficient in B complex vitamins, vitamin D, iron, and zinc. It is important that these minerals and vitamins be supplemented in a carbohydrate-free[34] and lactose-free product.[32]

All of the classic diets are supplemented with a multivitamin in addition to 600–650 mg of calcium daily. This replaces the mineral and vitamin deficiencies of the diet. It is essential that pharmacists determine the carbohydrate and lactose content of these supplemental products.

Indications for the Diet

It appears that the best candidates for the ketogenic diet are those who have refractory epilepsy or unacceptable side effects to standard AEDs. In addition, patients placed on the diet must have a strong support system at home to implement the diet because of its strict guidelines. Patients and family members must be willing to work closely with a dietitian to help make meal planning more realistic. Poor compliance can be partially eliminated with the help of a dietitian who is familiar with the diet.

Although in limited studies the best responders to the diet have been children, usually less than 10 years of age and greater than 1 year of age, this is not exclusive; the diet may be tried in other age categories as well.

Because of limited studies and studies that were completed before the International Classification System existed, it is hard to decide which types of epilepsy will respond best to the diet. In speculation, because of the stringent guidelines involved in following the diet and the side-effect profile in certain patients, the ketogenic diet should be reserved for those patients who are not responding to AED therapy. Once patients have optimal seizure control while on the diet (after a few months), concurrent AEDs may be slowly tapered to discontinuation.[12]

It appears that the anticonvulsant effect of the diet gradually increases over time, typically requiring several days to weeks.[13] As a rule of thumb, patients should be kept on the diet for at least 6 weeks before it is deemed a success or failure. If the dietary therapy is successful, it can be continued for 1–3 years or longer, if the patient and physician believe it is improving the patient's seizure control or AED side-effect profile.[35]

Resources

In many areas, state epilepsy foundations will be able to provide information on the ketogenic diet and recommend a support group for patients and family members. If the local affiliate does not have information or support networks, the Epilepsy Foundation of America (EFA) is a source of information (800-332-1000). Another good source is the Charlie Foundation to Help Cure Pediatric Epilepsy (800-FOR-KETO or 800-367-5386).

Practical guidelines also can be found on the Internet (URL: http://wwleland.standford.edu/group/ketodiet).[3]

Recommendations for Ketogenic Diet Therapy in Patients with Epilepsy

- Ketogenic diets should be reserved for patients who do not respond to adequate dosages or serum concentrations of standard AEDs or who have unacceptable adverse effects from standard AEDs.
- Patients on ketogenic diets should receive appropriate monitoring of electrolytes, complete blood counts, liver function tests, serum lipid panels, and carnitine levels.
- Patients on ketogenic diets should be maintained on carbohydrate-free and lactose-free vitamin and mineral supplements including vitamin D, a multiple-vitamin tablet containing B vitamins, calcium, magnesium, and iron.
- Pharmacists should provide information when necessary on carbohydrate and protein contents of prescription and nonprescription medications used in patients maintained on ketogenic diets.
- Pharmacists should act as liaisons between the pharmaceutical company and the patient, the patient's family, and the patient's physician to obtain necessary information on carbohydrate and protein contents of medications.
- Pharmacists should assist the family in home urinary measurement of ketones.
- Pharmacists should assist other members of the health care team in patient and family education regarding the ketogenic diet.

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