The Ketogenic Diet: A Practical Guide for Pediatricians

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ABSTRACT

The ketogenic diet is an effective treatment for drug-resistant epilepsies in children. In addition, it is the first-line treatment for some metabolic disorders, such as glucose transporter 1 deficiency syndrome. This article discusses the proposed mechanisms of a ketogenic diet's antiseizure action, its clinical indications, and its contraindications. The steps involved in ketogenic diet initiation, monitoring, and management of its side effects are also discussed. This review provides general pediatricians with the necessary skills to provide comprehensive care of children using the ketogenic diet and counsel their families and caregivers. **[*Pediatr Ann*. 2016;45(12):e446-e450.]**

Epilepsy is a common neurological disease in children, with an incidence of 41 to 187 per 100,000 children.[1] Although most cases of childhood epilepsies respond to seizure medications, one-third of patients develop drug-resistant epilepsy (DRE). In children with a resectable seizure focus, epilepsy surgery with targeted resection of the seizure focus is a viable treatment option, but there are patients who are not candidates for surgery. In these patients, the ketogenic diet (KD) has been used for epilepsy treatment for several decades, and it may be their best treatment option. In addition, it is the first-line treatment for some metabolic disorders, such as glucose transporter 1 deficiency syndrome (GLUTDS). There has been an increasing number of children placed on KD; therefore, an adequate knowledge of the diet is essential for every pediatrician caring for these children.

PROPOSED MECHANISMS OF ACTION

KD's mechanisms of action in controlling seizures remain under active research, but several theories have been proposed. The KD leads to fat metabolism in the liver that can be divided into three ketone bodies (KBs): beta-hydroxybutyrate (BHB), acetoacetate, and acetone. KBs cross the blood-brain barrier, are transported by the monocarboxylic acid transporter, and become the brain's primary energy source. During ketosis, there is more efficient synaptic removal of glutamate, the brain's major excitatory neurotransmitter. Its conversion to gamma-aminobutyric acid, a major inhibitory neurotransmitter, via the glutamate/gamma-aminobutyric acid–glutamine cycle leads to neuronal inhibition.[2] Acetoacetate and BHB inhibit glutamate neurotransmission by inhibiting activation of vesicular glutamate transporters.[3] KD also improves mitochondrial dysfunction associated with epileptogenesis.[4] Hyperactivity in the mammalian target of rapamycin pathway has been implicated in a variety of epilepsy models, including tuberous sclerosis complex, and it has been shown that KD may have anticonvulsant properties via mammalian target of rapamycin pathway inhibition.[5]

CLINICAL INDICATIONS AND CONTRAINDICATIONS

Treatment of DRE is the most common indication for KD. It is effective for both partial and generalized seizures. Studies have shown that 30% to 60% of patients with DRE who use the KD have at least a 50% reduction in seizure frequency at 6 months.[6] KD has also been found useful in some epileptic encephalopathies in young children, including Ohthahara syndrome, West syndrome, Lennox-Gastaut syndrome, and Dravet syndrome.[7] KD is the most effective treatment for Doose syndrome, a generalized epilepsy associated with myoclonic-astatic seizures.[8] KD al-

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lows successful weaning from continuous intravenous anesthetics in refractory status epilepticus.[9] It has also been used in patients with various metabolic disorders.[10] GLUTDS is characterized by seizures, developmental delay, and movement disorder due to absence of blood-brain glucose transporter, and KD is the treatment of choice because ketones use a different transport mechanism. In pyruvate dehydrogenase deficiency, glucose metabolism from pyruvate into acetyl coenzyme A (acetyl-CoA) is impaired, resulting in lactic acidosis. KD bypasses this metabolic block, lowers lactate production, and provides an alternative source of acetyl-CoA. Conversely, there are conditions such as primary carnitine deficiency, carnitine palmitoyl transferase deficiencies, carnitine translocase deficiency, beta-oxidation defects, pyruvate carboxylase deficiency, and porphyria where KD is contraindicated.[11]

CLASSIC KETOGENIC DIET AND OTHER DIETARY THERAPIES

Classic KD consists of 90% of calories from fat and only 10% from carbohydrates and proteins, resulting in a highly restricted diet (**Table 1**). Dieticians and caregivers, however, can be creative in preparing the meal (**Figure 1**). All-liquid KD formula is available and is used for formula-fed and gastrostomy tube-fed infants and children. The three other dietary therapies for epilepsy include the medium chain triglyceride diet (MCTD), modified Atkins diet (MAD), and low glycemic index diet (LGID). MCTD is based on the percentage of calories derived from MCT oil,[12] allowing more carbohydrates with increased palatability. However, it is associated with more gastrointestinal side effects such as vomiting, diarrhea, and bloating, and it is not recommended if the child is also taking valproic acid due to reports of liver failure when MCTD and valproic acid are combined. In MAD, carbohydrate intake is limited to 10 to 20 g/day, and the fat to protein and carbohydrate ratio is about 1 to 2:1.[13] LGID uses a more liberalized diet, with the carbohydrate limited to food with a glycemic index of <50.[14] The antiseizure efficacies of MCT, MAD, and LGID have been shown to be comparable with classic KD.[15-17]

TABLE 1.

Typical Ketogenic Diet Plan at a 3:1 Ratio[a] for a 5-Year-Old Patient

7:30 am Breakfast
- 70 g Heavy whipping cream[b]
- 20 g Strawberries, cantaloupe, or pineapple
- 40 g Scrambled eggs
- 4 g American cheese
- 8 g Butter

10 am Snack
- 27 g Heavy whipping cream[c]
- 17 g Strawberries, cantaloupe, or pineapple

12 pm Lunch[d]
- 70 g Heavy whipping cream[e]
- 20 g Cooked broccoli, green beans, or carrots
- 21 g Beef patty
- 7 g American cheese
- 7 g Melted butter (pour over vegetables)

3 pm Snack
- 27 g Heavy whipping cream[c]
- 90 g Sugar-free gelatin dessert

5:30 pm Dinner[d]
- 70 g Heavy whipping cream[e]
- 15 g Cooked broccoli, green beans, or carrots
- 19 g Grilled or baked chicken breast (no skin)
- 6 g American cheese
- 11 g Mayonnaise

[a]Ratio of fat to carbohydrate and/or protein.
[b]Whip the cream then weigh. Melt butter and mix with eggs, then make an omelet with cheese. Serve with water.
[c]Whip then weigh heavy whipping cream. Serve cream in a cup with lid and straw, and water.
[d]Serve with water, salt, and pepper
[e]Measure in milliliters and serve as a beverage.

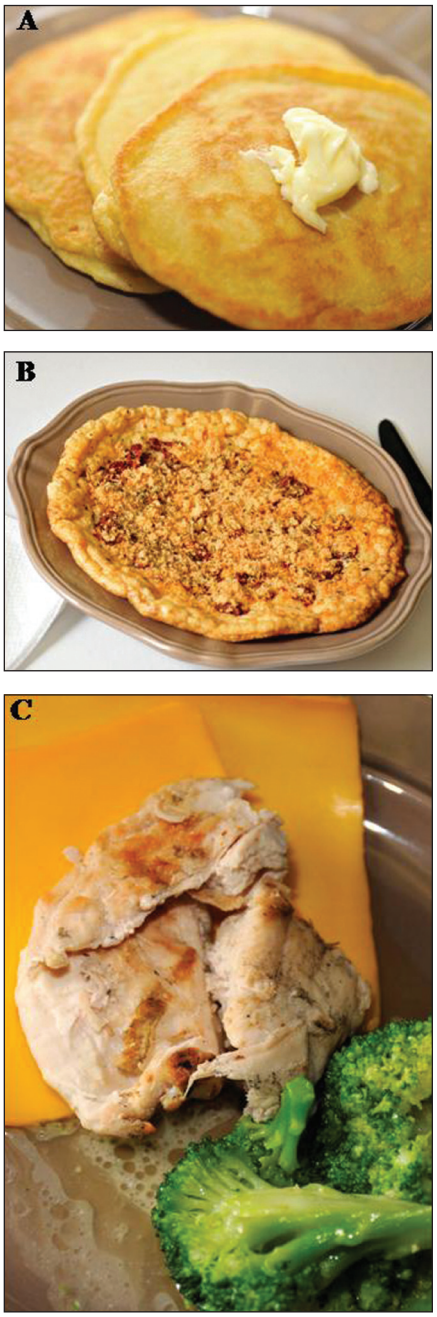

Figure 1. (A) Pancakes made of 30 g of macadamia nuts (ground into butter) with 28 g of egg, 6 g of canola oil, and 3 drops of vanilla extract. (B) Pizza made from 30 g of egg whites whipped into stiff peaks, with 17 g of macadamia nuts (ground into butter), 15 g of mayonnaise, 13 g of olive oil, 14 g of canned tomato puree, and 9 g of parmesan cheese. (C) A typical ketogenic diet meal consisting of cheese, chicken breast, and broccoli.

TABLE 2.

Recommendations for a Pre-Ketogenic Diet Evaluation

Counseling
Discuss seizure reduction, medication, and cognitive expectations
Identify potential psychosocial barriers to the use of KD
Review anticonvulsants and other medications for carbohydrate content
Recommend family reads parent-oriented KD information
Nutritional evaluation
Baseline weight, height, and ideal weight for stature
Body mass index when appropriate
Nutrition intake history: 3-day food record, food preferences, allergies, aversions, and intolerances
Establish diet formulation: infant, oral, enteral, or a combination
Decision on which diet to begin (MCT, classic, modified Atkins, or low glycemic index)
Calculation of calories, fluid, and ketogenic diet ratio (or percentage of MCT oil)
Establish nutritional supplementation products based on dietary reference intake
Laboratory evaluation
Complete blood count with platelets
Electrolytes to include serum bicarbonate, total protein, calcium, zinc, selenium, magnesium, and phosphate
Serum liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine)
Fasting lipid profile
Serum acylcarnitine profile
Urinalysis
Urine calcium and creatinine
Anticonvulsants drug levels (if applicable)
Urine organic acids
Serum amino acids
Ancillary testing (optional)
Renal ultrasound and nephrology consultation (if a history of kidney stones)
EEG
MRI
Cerebrospinal fluid if no clear etiology has been identified
EKG (echocardiogram) if history of heart disease

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; EEG, electroencephalogram; EKG, electrocardiogram; KD, ketogenic diet; MCT, medium chain triglyceride; MRI, magnetic resonance imaging.
Reprinted with permission from Kossoff et al.[11]

INITIATION OF KETOGENIC DIET

A visit with the dietician is recommended for counseling as well as for nutritional and laboratory evaluation before beginning the KD.[11] A swallowing evaluation may be needed in children with severe neurological impairment. Laboratory evaluation is necessary prior to diet initiation and while the patient is using the KD. The International Ketogenic Diet study group[11] recommends several prerequisites (**Table 2**) prior to initiation of the KD. Basic metabolic diagnostic evaluation should be done to exclude metabolic disorders that may contraindicate its use (**Table 2**). A KD-trained dietician calculates the diet with the goal of creating and maintaining ketosis. Classic KD is initiated during a hospital stay because metabolic complications may occur during diet initiation.[11] Traditionally, a fasting period of 24 to 48 hours is used to rapidly induce ketosis; however, a randomized controlled trial[18] suggested that gradual diet initiation without fasting does not change the long-term seizure control outcome and is associated with fewer adverse effects. Although more immediate seizure control is achieved with the fasting approach,[19] we use the nonfasting, gradual KD initiation and typically start with a fat to carbohydrate and protein ratio of 1:1 followed by daily advancement to 2:1, then to 3:1; if necessary the ratio can be increased to 4:1. During the process, blood glucose, urine ketones and urine specific gravity, serum BHB, and electrolytes are monitored. The child's home medications should be switched to the lowest sugar-containing formulations. Both intake and output are carefully monitored. Anthropometric measurements are also monitored. During the hospital stay, families and caregivers are given intensive education on meal preparation and monitoring for side effects. It is recommended that KD should be tried for at least 3 months to test for efficacy.[11] For children who respond with at least 50% seizure reduction, the diet should be continued for at least 2 years. Children using KD should be evaluated in the clinic every 1 to 3 months.

KETOGENIC DIET SIDE EFFECTS: MONITORING AND MANAGEMENT

Metabolic Disturbances

Metabolic abnormalities such as dehydration, hypoglycemia, excessive ketosis, metabolic acidosis, and electrolyte imbalance are among the common

metabolic side effects of KD. Dehydration is more common in protocols that include fasting. In general, blood glucose of <40 mg/dL and symptomatic hypoglycemia are treated with carbohydrate-containing beverages such as orange juice. Side effects of decreased activity and gastrointestinal symptoms such as abdominal pain and vomiting are usually transient and rarely require diet discontinuation, but may require reducing the KD ratio.[18]

Gastrointestinal Symptoms

KD's high-fat content prolongs the gastric emptying time and can cause vomiting. Constipation occurs due to low fiber and food intake. KD at a 3:1 ratio is associated with fewer gastrointestinal symptoms compared to the 4:1 ratio.[20] Hepatitis and pancreatitis are rare yet fatal complications,[21] so extra caution is recommended in patients who take antiepileptic medications such as valproic acid.

Kidney Stones

KD-associated risk of kidney stones range from 2% to 6% and may be as high as 25% in those who have been on KD for longer than 6 years.[22] Administration of potassium citrate can reduce the risk to .9%.[23] Despite the independent risk for kidney stone development associated with use of carbonic anhydrase inhibitors (eg, topiramate and zonisamide), its concurrent administration with KD does not appear to increase the risk.[24] Measurement of urinary calcium-to-creatinine ratio at baseline and every 3 months is recommended. Renal ultrasound should be considered if there are signs and symptoms concerning for kidney stones.

Growth Failure and Vitamin and Mineral Deficiencies

Growth failure may occur in children on KD,[25] and it is treated by lowering the KD ratio.[19] Vitamin and mineral deficiencies have been reported.[11] Calcium and vitamin D deficiency can lead to osteopenia and osteoporosis. Periodic dual energy X-ray absorptiometry screening should be considered in children using long-term KD. The use of low-carbohydrate multivitamins with minerals and calcium along with vitamin D supplementation is recommended.[11] Carnitine deficiency may occur and supplementation may be needed.

Dyslipidemia and Cardiovascular Complications

Cardiomyopathy and corrected QT interval prolongation have been seen in children on KD, and the underlying mechanism may be selenium deficiency.[26] Checking whole blood selenium levels before and while on KD is recommended. KD may cause hypercholesterolemia, hypertriglyceridemia, and elevation of apolipoprotein B-containing lipoprotein.[27] The long-term effect of KD-induced dyslipidemia on vascular structure and atheroma formation remains unclear. Although it appears to have no effect on the carotid intima-media thickness and elastic properties after 12 months of KD treatment,[28] Doppler studies and echocardiogram may be necessary in the presence of chronic dyslipidemia and to screen for cardiomyopathy. A higher proportion of unsaturated to saturated dietary fats, the addition of MCT oil, a lower KD ratio, and carnitine supplementation may help prevent the risk of dyslipidemia.[19]

Special Situations

Most children consuming a KD have comorbid medical issues. Special care is needed when they are admitted to the emergency department or hospitalized. The use of dextrose-containing intravenous fluids is a common cause of seizure relapse in these children and should, therefore, be avoided. In an intensive care unit, KD should be avoided in children receiving propofol infusion due to the risk of fatal propofol infusion syndrome.[29] Over-the-counter medicines may have carbohydrates and can lead to ketosis reversal and seizure breakthroughs. Adequate counseling of the patient's caregiver is necessary. Children on KD can safely undergo general anesthesia for surgical procedures; however, close monitoring for hypoglycemia and metabolic acidosis is needed.[30]

CONCLUSION

KD is a proven and effective treatment for seizures in children. However, it requires adequate and close monitoring of growth and laboratory parameters. Diet adjustment may be needed to assist growth and nutritional status while maintaining seizure control. The combined efforts of pediatric neurologists, pediatricians, and dieticians in monitoring children on KD are essential to the success of KD therapy and to the prevention, recognition, and treatment of its side effects.

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