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Ketogenic Diets: An Update for Child Neurologists

Eric H. Kossoff, MD, Beth A. Zupec-Kania, RD, and Jong M. Rho, MD

The ketogenic diet, modified Atkins diet, and low-glycemic-index treatment have all emerged over the past decade as important therapeutic options for children with intractable epilepsy. Whereas only a decade ago the ketogenic diet was seen as an "alternative" treatment of last resort, it has become more frequently used throughout the world. The past year alone 2 randomized and controlled trials of the ketogenic diet were published, as well as the use of the ketogenic diet for new-onset epilepsy (infantile spasms), and a 26-member international consensus statement guiding optimal clinical management. There has been an equally dramatic increase of interest into mechanisms of action using various experimental models. Researchers are also highly interested in using diets for neurologic disorders other than epilepsy, including autism and brain tumors. This review will update child neurologists on the recent advances in the use of ketogenic diets.

Keywords: ketogenic diet; epilepsy; Atkins; ketosis

I n 1921, Dr Rawle Geyelin gave a presentation at the annual meeting of the American Medical Association.[1] He reported the outcomes of several children who had benefited from fasting, often with long-lasting reduction in their seizures. Wilder continued this work by creating a "ketogenic diet" that mimicked the effects of fasting but was formulated as a tolerable, reproducible, high-fat, and low-carbohydrate diet.[2] For the next 20 years, largely as a result of researchers at the Mayo Clinic in Rochester, Minnesota,[3] the ketogenic diet became a popular and well-studied treatment for both children and adults with epilepsy.

As anticonvulsants such as phenytoin (and later carbamazepine and valproate) were introduced to the United States, the ketogenic diet fell out of favor and was only used at a few academic centers. In November 1993, a 20-month-old boy from California named Charlie Abrahams was treated at Johns Hopkins Hospital after failure to respond to multiple anticonvulsants and surgery for his complex partial seizures. The ketogenic diet led to seizure freedom within days and his father, Jim, created The Charlie Foundation the following year to promote research, as well as clinical awareness and availability of the ketogenic diet.

The past 15 years have witnessed an enormous growth of interest in the ketogenic diet. At this writing, a PubMed search indicates that nearly 750 peer-reviewed articles on the ketogenic diet have been published since 1994. In 2006, symposia at both the International Child Neurology Association and Child Neurology Society annual meetings were the first sessions ever held devoted solely to the ketogenic diet. In April 2008, a 4-day international conference devoted to the use of dietary treatments brought 270 attendees to Phoenix, Arizona. The ketogenic diet is now available in over 50 countries, in all continents except Antarctica.[4] As a direct result of this growing interest, an expert consensus guideline was commissioned by The Charlie Foundation, written by 26 neurologists and dietitians from 9 countries, endorsed by the Child Neurology Society, and published in *Epilepsia* in November 2008.[5] This consensus guideline was designed not only to suggest the optimal management of children receiving the ketogenic diet but also to highlight aspects of dietary treatments that were unclear and potentially areas of future research.[5]

This review was written on behalf of The Charlie Foundation on the 15th anniversary of its creation to inform child neurologists of the remarkable advances in the use of the ketogenic diet since 1994. Research has demonstrated how well the ketogenic diet works overall as well as specific indications in which it may be even more

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effective. Animal studies have helped clarify insights into its mechanisms of action, which may ultimately guide clinical use. Contrary to prior common beliefs that the ketogenic diet is unpalatable and intolerable, dietitians have worked diligently to create meal plans for all cultures. In addition, researchers have studied different methods of starting the ketogenic diet (eg, nonfasting and outpatient initiations), alternative dietary treatments that allow more calories, fluid, and protein (eg, the modified Atkins diet and low-glycemic-index treatment), and treatments to prevent adverse effects. Last, neurologists other than epileptologists have taken notice of the ketogenic diet and are actively studying it for nonepilepsy uses.

What Exactly Are the Ketogenic Diets?

The classic ketogenic diet—also known as the long-chain triglyceride diet—has been the traditional treatment and the one that for which there is the most clinical data. In this formulation, fat provides the majority of calories, protein is based on minimum daily requirements, and carbohydrates are severely restricted. The classic ketogenic diet is determined by a ratio of grams of fat to grams of protein plus carbohydrate combined. A 4:1 ratio (90% calories from fat) is typically used for children, although a 3:1 ratio (86% fat) or a 2:1 (83% fat) may be necessary to ensure sufficient protein in adolescents and infants and for children with exceptionally low energy needs. Calories are controlled initially to 80% to 90% of the daily recommendations for age but are frequently adjusted over time to accommodate ideal growth and satiety. Fluid restriction is no longer considered necessary, and adequate fluid intake is probably preventative of constipation and kidney stones, both of which are not uncommon adverse effects of the ketogenic diet.

The medium-chain triglyceride, although not as commonly used in the United States, has been shown to have similar efficacy to the classic ketogenic diet.[6,7] A greater allowance of carbohydrate and protein, and 10% to 20% fewer calories from fat is provided because medium-chain triglycerides yield more ketones per kilocalorie of energy than long-chain triglyceride diets. Centers that have used both diets find benefits in incorporating medium-chain triglyceride into the classic ketogenic diet for its laxative effects and improved tolerance from liberalization of the carbohydrate content of the diet. This tasteless oil can be mixed into foods and can be also consumed as a "medication." The medium-chain triglyceride oil, however, can be more expensive than butter and vegetable oils and is not reimbursable by insurance companies, which limits its use to some families. A typical meal plan for the ketogenic diet is described in Table 1.

During the course of treatment, the ketogenic diet is generally adjusted to accommodate optimal growth for the

Table 1. Example of Typical Ketogenic Diet Meals Using a 1100 kcal, 4:1 Ketogenic Diet (for a Typical 4-Year-Old Child)

Breakfast
  90 g ketogenic pudding
  44 g cream cheese
  13 g eggs
  29 g heavy cream
  10 g strawberries
Lunch
  40 g 36% heavy cream
  8 g medium-chain triglyceride oil (mixed into cream)
  Dark meat chicken salad
    20 g dark meat chicken
    8 g mayonnaise
  20 g avocado
Dinner
  35 g 36% heavy cream
  Ground beef and cheese
    11 g ground beef
    10 g cheese
    8 g butter
  26 g cooked broccoli
  11 g butter
Snack
  Ketogenic chocolate candy
    3 g cocoa
    6 g butter
    6 g coconut oil

child. Although there is no clear evidence in humans of the need for caloric restriction, avoidance of excessive calories may anecdotally improve efficacy. Fine-tuning methods include adjusting calories or the ratio, or incorporating medium-chain triglyceride oil into the diet to produce higher levels of ketosis, which may be helpful for some individuals. Coconut oil, a less expensive alternative to medium-chain triglyceride oil, can also be used in these diets. Another fine-tuning step is to eliminate processed foods, which are less specific in macronutrient content than natural foods. Sugar alcohols, which are partially absorbed, should also be avoided.

The ketogenic diet may also be administered as a formula-based diet for infants and for enterally fed individuals. Formula preparation and administration are relatively simple, and commercial products are available for this purpose (Table 2). Formula-fed individuals (including via gastrostomy and jejunostomy tubes) receive the benefit of excellent compliance and higher efficacy in some studies than individuals fed a solid ketogenic diet.[8,9]

Modernization of the ketogenic diet has led to 2 new dietary therapies in the past decade: the modified Atkins diet and low-glycemic-index treatment.[10-13] Similar to the classic ketogenic diet, these diets are high in fat (approximately 65%) and restricted in carbohydrate. They are initiated as an outpatient and require more caregiver independence in designing meals and researching appropriate foods. Initial reports of small uncontrolled trials

Table 2. Ingredients of 2 Commercially Available Ketogenic Liquid Formulations

	Quantity	Fat (g)	Protein (g)	Carbohydrate (g)	Kilocalories	Ratio
Formula #1						
KetoCal powder (Nutricia)	139 g	100	21	4	1000	4:1
Water	860 mL	0	0	0	0	
Formula #2						
Ross carbohydrate-free (Abbott)	440 mL	31.7	17.6	0.04	356	
Microlipid (Nestle)	137 mL	68.5	0	0	617	
PolyCal (Nutricia)	8 g	0	0	7.7	31	
Water	425 mL	0	0	0	0	4:1
					(total = 1004)	

Table 3. Comparison of the 4 Major Ketogenic Diets in Clinical Use (1000 kcal/d Provided)

Diet	Fat (g)	Protein (g)	Carbohydrate (g)
Classic long-chain triglyceride			
4:1	100	17	8
3:1	96	18	14
2:1	92	20	26
1:1	77	37	40
Medium-chain triglyceride oil diet	78	25	50
Low-glycemic-index treatment	67[a]	40-60[a]	40-60
Modified Atkins diet	72[a]	68-78[a]	10-20

[a] Values are approximate.

indicate that 40% to 50% of patients (both children and adults) will have >50% seizure reduction after 3 to 6 months.[10-15] These diets may have a particular benefit for adults and patients in developing countries.[16,17] Table 3 compares the fat, protein, and carbohydrate content of the aforementioned diets.

Evidence for Efficacy

How well do dietary therapies actually work? Over the past 88 years since its introduction, the ketogenic diet has been shown to be extremely successful in both retrospective and prospective studies. Early data described 75% to 90% of children having a 50% seizure reduction.[18] More recent publications, involving larger numbers of patients, have not confirmed this level of response. Compared to vagus nerve stimulation, the other major nonpharmacologic treatment for intractable epilepsy, the ketogenic diet appears to work faster, typically within 2 to 4 weeks compared to several months.[19,20] Some epileptologists have argued that the ketogenic diet may be one of the most effective therapies for childhood-onset epilepsy other than surgery (assuming surgical resection is a possibility).

In the past decade, there have been 4 major meta-analyses of the efficacy of the ketogenic diet, all of which determined that there is clear evidence for benefit despite the lack of blinded, controlled trials at the times of publication.[21-24] In 2000, Lefevre and Aronson[21] systematically reviewed 11 ketogenic diet studies and identified a 56% responder rate (>50% reduction in seizures), 32% of whom had >90% seizure reduction. They concluded "although controlled trials are lacking, the evidence is sufficient to determine that the ketogenic diet is efficacious in reducing seizure frequency in children with refractory epilepsy."[21] After 4 years, a Cochrane review of 14 studies commented on the lack of double-blind, controlled trials but stated "for those with a difficult epilepsy on multiple antiepileptic drugs, we consider the ketogenic diet a possible option."[22] In 2006, 2 reviews by Keene[23] and Henderson and colleagues[24] were performed. The meta-analysis of 19 studies by Henderson and colleagues, providing a total of 1084 patients,[24] confirmed that the ketogenic diet reduced seizures by >90% in a third of the patients and by >50% in half. There was no clear influence of age, seizure type, or etiology on seizure reduction overall.

Although all 4 of these reviews commented on the lack of class I and II data, this became no longer valid in 2008. A clinical trial conducted at the Institute for Child Health in London by Neal and colleagues[25] randomized children to receive the ketogenic diet, either after a 1-month (treatment group) or 4-month delay (control group) with no additional anticonvulsant changes. These investigators found that the seizure frequency after 4 months was significantly lower in the 54 children on the ketogenic diet (38% decrease in seizures), compared to the 49 controls (37% *increase* in seizures; $P < .0001$).[25] No child in the control group had a >90% reduction in seizures, compared to 5 with the ketogenic diet ($P = .06$).[25] No difference was seen in efficacy between the classical- and medium-chain triglycerides diets, the latter which was also a randomized arm of this trial.[7]

Another randomized controlled study was published this year and was specific for children with Lennox Gastaut syndrome treated at Johns Hopkins Hospital.[26] Investigators were able to successfully blind parents, patients, and physicians using a saccharin (treatment) versus glucose (placebo) crossover design following two 36-hour

fasts separated by 6 days at ketogenic diet initiation. Unfortunately, ketosis was observed even in the placebo group, and fasting twice over this study period likely prevented a true return to a baseline state; results only neared statistical significance in favor of treatment ($P = .07$).[26] There was overall a mean decrease of 34 seizures per day over the 12-day study period ($P = .003$).[26]

The modified Atkins diet and low-glycemic-index treatment also have demonstrated short-term efficacy for intractable epilepsy. The modified Atkins diet has also been studied in 11 prospective and retrospective studies from 5 centers to date.[10,11,14-17,27-31] Of the 126 children and adults that have been reported, 54 (43%) had a >50% seizure reduction. Thirty-four (27%) had >90% seizure reduction, which is very similar to the percentage often quoted for the ketogenic diet.[24] When successful, the modified Atkins diet works within 2 to 4 weeks.[16,19]

Two formal retrospective studies of the low-glycemic-index treatment have been published, and 10 (50%) of 20 children had >90% seizure reduction in the first.[12] In 2009, the authors updated their results with a total of 76 children, with results after 1 month demonstrating a 50% reduction in seizures in approximately 50% of children.[13] Similar to the modified Atkins diet, ketosis did not correlate with seizure control, although serum ketone levels were higher than baseline at all time-points.[13] At 1 and 12 months on the low-glycemic-index treatment, lower serum glucose levels were significantly associated with likelihood of >90% seizure reduction.[13] Additional studies of both diets are currently underway, but due to their relatively recent introduction, there is limited information regarding their long-term efficacy, which patients should be started initially on these diets, and when to switch patients to the ketogenic diet if unsuccessful.

Other benefits beyond seizure control have been reported and are often primary reasons for parents to start the ketogenic diet.[32] Weight loss can occur and may be beneficial.[16] Some children also show improvements in development and behavior.[33] Anticonvulsants are frequently reduced in dosage or even discontinued if the ketogenic diet is successful, and this is one of the most common requests of parents at ketogenic diet initiation.[32] The effects of the ketogenic diet can be long lasting, and many children who have seen benefit can return to a normal diet after several years without resumption of seizure activity.[34,35]

Mechanisms of Action

Understanding how the ketogenic diet works is one of the perplexing mysteries in epilepsy research. The fact that the ketogenic diet exerts broad-spectrum clinical efficacy against heterogeneous seizure types and epilepsy syndromes implies that a fundamental common molecular pathway responsible for dampening neuronal hyperexcitability and hypersynchrony must be critically involved. Furthermore, unlike anticonvulsants that are traditionally believed to act on cellular membrane-bound ion channels and transporters, or on neurotransmitter enzymes,[36] the ketogenic diet acts on a multiplicity of novel molecular targets that respond to a fundamental shift from glycolysis to fatty acid oxidation. At this juncture, despite many hypotheses that have been advanced to explain the anticonvulsant (and potentially, neuroprotective) effects of the ketogenic diet, none have been substantiated or universally accepted.[37-39]

Nevertheless, efforts at determining the underlying mechanisms of ketogenic diet action have continued to amplify the emerging notion that modulation of fundamental biochemical pathways can produce anticonvulsant effects in vivo. The hallmark feature of ketogenic diet therapy, and indeed the established clinical marker of altered metabolism, is ketosis, a consequence of increased fatty acid oxidation. Ever since the inception of the ketogenic diet, investigators have attempted to validate the potential anticonvulsant activity of ketone bodies themselves (ie, β-hydroxybutyrate, acetoacetate, and acetone). In support of this, acute administration of acetoacetate and acetone blocked seizure activity induced by maximal electroshock and pentylenetetrazole in normal rats[40] and protected against audiogenic seizures in nonepileptic mice.[41] These studies validate the historical observation by Keith[42] that in normal rabbits, acetoacetate was protective against seizures induced by thujone, a γ-aminobutyric acid (GABA$_A$) receptor antagonist. Interestingly, there are as yet no consistent data demonstrating acute anticonvulsant effects of the major ketone body, β-hydroxybutyrate, despite the fact that it is rapidly interconverted to acetoacetate via a dehydrogenase enzyme.

Whether ketone bodies exert direct anticonvulsant actions in a chronically epileptic brain also remains controversial. Nonetheless, Ma et al[43] have recently reported that ketone bodies, in a use-dependent manner, decreased the spontaneous firing rate of GABAergic neurons in the rat substantia nigra pars reticulata via activation of plasmalemmal or surface ATP-sensitive potassium channels. This, in turn, induces membrane hyperpolarization. The suggestion was made that such modulation may dampen neuronal excitation in other seizure-prone brain regions, in line with previous studies, indicating that the substantia nigra functions in part as a central "seizure gate." However, the relevance of this finding to the mechanism of ketogenic diet action remains unclear. In implicating surface ATP-sensitive potassium channels, one must reconcile the fact that the ketogenic diet can increase levels of ATP and other bioenergetic substrates through enhanced mitochondrial respiration.[44,45] Because high ATP levels block surface ATP-sensitive potassium channel activity, it is unclear how the opening of these channels could be

achieved by infusion of ketone bodies in the substantia nigra pars reticulata.

Along related lines, 2-deoxyglucose, an inhibitor of phosphoglucose isomerase, the enzyme that converts glucose-6-phosphate to fructose-6-phosphate, has been shown to be broadly effective against multiple animal models of seizures and in kindling models of temporal lobe epilepsy.[46,47] More recently, Lian et al[48] demonstrated that fructose-1,6-bisphosphate, a metabolite that shifts the metabolism of glucose from glycolysis to the pentose phosphate pathway, exhibits potent anticonvulsant activity in several rat models of acute seizures (ie, pilocarpine, kainic acid, and pentylenetetrazole), and efficacy in these models actually exceeded that of either substantia nigra pars reticulata or ketogenic diet treatment. Collectively, these data indicate that the overall strategy of limiting glycolytic flux may be a powerful way of preventing acute seizures and perhaps epileptogenesis. Whether glucose restriction allows for a compensatory increase in fatty acid oxidation or enhanced flux of tricarboxylic acid intermediates (eg, anaplerotic substrates) remains to be firmly demonstrated.

In approximately 20% of patients, anticonvulsant medications can be successfully discontinued without recrudescence of seizures.[35,49] In one study of 41 children who discontinued the ketogenic diet prior to 1-year diet duration, and who did not have later epilepsy surgery or vagus nerve stimulation, a surprising 19 (46%) had >50% seizure reduction 3 to 6 years later.[35] It is this anecdotal clinical observation that forms the basis for the intriguing hypothesis that the ketogenic diet may possess neuroprotective and/or antiepileptogenic properties.[50,51] However, it is extremely difficult to determine whether patients who remain seizure-free after cessation of a ketogenic diet have had spontaneous remission of their epilepsy or have experienced a true direct antiepileptogenic (or disease-modifying) effect. By contrast, in experimental models, the ketogenic diet and its metabolites appear to have consistent neuroprotective actions, suggesting that this therapeutic strategy may preserve neuronal integrity in addition to reducing spontaneous recurrent seizures.[50]

Who Should Be Started on the Ketogenic Diet?

Not long ago, the general advice given by ketogenic diet experts to child neurologists considering a referral for the ketogenic diet was that all children were equally likely to respond. It is known that children with glucose transporter protein 1 deficiency and pyruvate dehydrogenase deficiency required the ketogenic diet for normal development, and those with pyruvate carboxylase deficiency, fatty acid oxidation defects, primary carnitine deficiency, porphyria, and several mitochondrial disorders

Table 4. Potential Beneficial Indications for Dietary Therapy (Adapted From Ref 5)

Probable Benefit (at Least 2 Publications)
Glucose transporter protein 1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Myoclonic-astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Infantile spasms
Selected mitochondrial disorders
Children receiving only formula (infants or enterally fed patients)
Suggestion of benefit (one case report or series)
Landau-Kleffner syndrome
Lafora body disease
Combined use with vagus nerve stimulation
Combined use with zonisamide

should not be placed on the ketogenic diet.[5] However, it was often stated that no specific seizure syndromes or particular conditions (other than metabolic concerns) were either more or less likely to have a beneficial response. This no longer appears to be true today.

The ketogenic diet has been shown to be particularly effective in myoclonic-astatic epilepsy (Doose syndrome),[52] tuberous sclerosis complex,[53] and several other epileptic conditions (Table 4). It is so effective for infantile spasms that investigators at Johns Hopkins published their retrospective experience this past year using the ketogenic diet for infantile spasms before any anticonvulsants or steroids were used.[54] The ketogenic diet was successful within 2 weeks in 9 of 13 (62%) and was associated with fewer recurrences and side effects when compared to a cohort of infants treated with adrenocorticotrophic hormone.[54] Children receiving an all-formula ketogenic diet (eg, gastrostomy tube-fed patients or infants) also appear to do extremely well.[8,9] Additionally, children receiving either concurrent vagus nerve stimulation or zonisamide may show preferential benefit when the ketogenic diet is started.[55,56]

Conversely, children with partial seizures appear less likely to respond to the ketogenic diet.[57] This is especially true if the given child is a candidate for epilepsy surgery. In 2 studies, surgery led to seizure-free responses in 59% to 63% of children compared to 0% to 17% with the ketogenic diet.[57,58] There are many ketogenic diet experts who will not offer this therapy to children who are candidates for surgery, even when seizures are refractory to medications, based on this large difference between results.[5] The decision, however, should be made in combination with the parents and patient's wishes, in our opinion. Last, recent evidence suggests that the ketogenic diet may work less well in those receiving phenobarbital.[56]

When should child neurologists refer a patient or start the ketogenic diet? In general, most ketogenic diet experts will generally recommend starting the ketogenic diet after

Table 5.   Resources for Child Neurologists, Dietitians, Patients, and Parents

Books
  Freeman JM, Kossoff EH, Freeman JB, et al. *The Ketogenic Diet: A treatment for epilepsy in children and others.* 4th ed. New York: Demos; 2007.
  Zupec-Kania BA. *Ketogenic Diet: Parent's Guide.* Santa Monica, CA: The Charlie Foundation; 2009.
  Snyder D. *KetoKid.* New York: Demos; 2006.
  Stafstrom CE, Rho JM. *Epilepsy and the Ketogenic Diet.* Totowa, NJ: Humana Press; 2004.
Web sites
  The Charlie Foundation: (www.charliefoundation.org)
  Matthew's Friends: (site.matthewsfriends.org)
  KetoCalculator: (www.ketocaluclator.com)
  Keto News (Monthly Newsletter): (www.epilepsy.com/ketonews)
  My KetoCal: (www.myketocal.com)
  Atkins diet recipes: (www.atkins.com/Recipes.aspx)

2 appropriate anticonvulsants have been previously tried and failed.[5] Children listed in Table 4 should be referred sooner for its consideration. In our experience, parents are remarkably appreciative of the earlier consideration of dietary treatment, even if they decide not to pursue it at a given time.

How Should the Ketogenic Diet Be Initiated?

Prior to the initiation of dietary therapies, it is essential for the family to meet with a clinical dietitian to review the child's growth history and current dietary intake to determine if there are difficulties with the ability to maintain nutrition or consume adequate fluid.[5] Children with severe neurological impairments may require a swallow evaluation to ensure consistent nutrition and fluids. The carbohydrate content of the child's medications should be reviewed and changed to the lowest carbohydrate formulations to minimize this potential source of carbohydrates. The family can help prepare their child for the diet by providing balanced meals, sufficient fluids, and eliminating foods that contain added sugar. Educational information should be presented to the family to prepare them for the commitment of managing a restrictive diet. Helpful resources are included in Table 5.

The ketogenic diet is traditionally preceded by a fasting period of 12 to 48 hours to stimulate ketosis. Fasting is no longer considered necessary to start the ketogenic diet according to 2 recent studies showing similar efficacy at three months with or without fasting.[59,60] However, some data suggest a more immediate improvement in seizure control (median of 9 days more quickly) with a fasting approach.[19] The incidence of vomiting appears identical with either approach.[60] Even without fasting, the incidence of hypoglycemia, acidosis, nausea, dehydration, or

metabolic complications due to an undetermined metabolic disorder may occur. For these reasons, the ketogenic diet is typically administered under medical supervision in a hospital setting.[5] The ketogenic diet may be introduced in incremental doses such as advancing by one third of targeted calories each day over a 3-day period. Another method is to begin at full calories and increase the ratio daily (from 1:1, 2:1, 3:1, to 4:1).[60] During the ketogenic diet initiation week, the family receives intensive education on preparing and weighing meals, vitamin and mineral supplementation, fluid goals, handling illness, and how to monitor for adverse effects. Families are discharged with carbohydrate-free medication prescriptions and follow-up appointments are arranged (every 3 months for most children; every month for infants initially).[5]

Adverse Effects

Long-term adverse effects of the ketogenic diet have been reported and include growth retardation,[61-63] gastrointestinal symptoms,[64] carnitine deficiency,[65] kidney stones,[66-68] and elevated lipids.[64,69-71] Additional serious adverse effects have been reported in a small number of patients and include cardiac abnormalities due to selenium deficiency,[64,72-74] Fanconi renal tubular acidosis,[75] and pancreatitis.[64,76] Children receiving the ketogenic diet continuously for >6 years are at high risk for kidney stones, bone fractures, and growth disturbances but not dyslipidemia.[63]

A recent analysis of a 4:1 ketogenic diet revealed that despite the inclusion of nutritious foods, this diet provided less than the dietary reference intake for 19 of 23 micronutrients.[77] Prevention of nutrition-related adverse effects may be achieved through appropriate vitamin and mineral supplementation. A supplement profile containing vitamins, minerals, and trace minerals to meet the dietary reference intakes is recommended.[5] Supplements should be carbohydrate-free or contain minimal carbohydrate. Children who have received anticonvulsants are at risk for osteoporosis, and this effect can be compounded by the ketogenic diet.[78] These children may require an evaluation by an endocrine specialist who may recommend therapeutic doses of vitamin D and minerals. The need for medical and nutritional surveillance of children during the course of therapy is clearly warranted (Table 6).

Attempts to prevent adverse effects from the ketogenic diet have only been met with partial success. Growth remains problematic, especially in the youngest children.[61,79] Growth disturbance is often treated with lowering the ketogenic ratio; however, in 1 study that did not lead to improved growth, high levels of ketosis were suspected as the culprit.[80] Dyslipidemia improves with additional medium-chain triglyceride oil, lower ketogenic ratios, and carnitine, yet the improvement seen in 1 study

Table 6.   Prediet Evaluation and Follow-Up Care (Adapted From Kossoff 2008)[5]

Counseling
   Discuss seizure reduction, medication, and cognitive expectations
   Identify potential psychosocial barriers to the use of ketogenic diet
   Review anticonvulsants and other medications for carbohydrate content
   Recommend family read parent-oriented ketogenic diet information
Nutritional evaluation
   Baseline weight, height, and ideal weight for stature
   Body mass index (BMI) 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 (medium-chain triglyceride, classic, modified Atkins, or low-glycemic-index treatment)
   Calculation of calories, fluid, and ketogenic 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
   Anticonvulsant drug levels (if applicable)
   Urine organic acids
   Serum amino acids

Note: ALT, alanine aminotransferase; AST, aspartate aminotransferase; MCT, medium chain triglyceride.

Table 7.   Non-Epilepsy Uses of Ketogenic Diets Published in the Literature to Date (Alphabetical Order)

ALS
Alzheimer disease
Autism
Bipolar disorder
Brain tumors
Depression
Diabetes
Glycogenosis type V
Migraine
Narcolepsy
Obesity
Parkinson disease
Post hypoxic myoclonus
Schizophrenia
Sleep disorders
Stroke
Traumatic brain injury

Note: ALS, amyotrophic lateral sclerosis.

was not statistically significantly higher than observation alone.[71] Interestingly, those children receiving a formula-only ketogenic diet did have lower total cholesterol values than those on fully solid ketogenic diets.[71] Last, the risk of kidney stones was reduced from 6.7% to 0.9% with the addition of oral citrates (Polycitra K) at ketogenic diet onset in 1 recent study.[81] Oral citrates increase urine pH but do not affect serum CO_2 levels.[81]

Diet Discontinuation

The consensus guideline stated that the ketogenic diet should be used for at least an average of 3.5 months before discontinuation due to reasons of inefficacy.[5] For children who remain on the diet and achieve >50% seizure response, the ketogenic diet is often continued for at least 2 years (unless there is a serious adverse effect that cannot be corrected). Children who achieve >90% seizure control have been reported to remain on the ketogenic diet for up to 12 years.[63] There is 1 report which revealed that of the children who achieved seizure freedom with the ketogenic diet, 80% remained seizure-free when the ketogenic diet

was stopped after typically 2 years.[34] The risk of seizure recurrence was higher in those who had epileptiform electroencephalographies (EEGs), structural abnormalities on neuroimaging, and tuberous sclerosis complex.[34] The ketogenic diet can be weaned immediately in cases of emergency or more typically over weeks by reducing the ratio gradually in those who have been treated for years. Should seizures significantly increase in this latter situation, the ratio can be increased again and the ketogenic diet maintained.

Future Uses of Ketogenic Diets

The concept that the ketogenic diet may be neuroprotective has broad-reaching implications for other neurological disorders characterized either by neurodegeneration or by metabolic derangement.[82] In this regard, while there is at present a noteworthy absence of clinical data in comparison to epilepsy, there is an expanding experimental literature suggesting that the ketogenic diet (and/or its metabolites) may be an effective treatment for several neurologic conditions (Table 7). Clinical trials in humans are ongoing for Alzheimer disease, amyotrophic lateral sclerosis, migraine, and brain tumors, based on early research.[83-86] It is unknown whether the mechanisms of action that have been theorized for the ketogenic diet's beneficial effects against epilepsy may be the same for these other neurologic disorders. As these "alternative" uses for the ketogenic diet continue to be explored, child neurologists and dietitians will be increasingly asked to provide guidance for patients with neurologic conditions being treated with the ketogenic diet on an experimental basis. Whether busy child neurologists already in short supply can handle this increase in patient demand is unclear.[87]

Conclusions

The ketogenic diet remains one of the most effective, yet underused treatments for intractable childhood epilepsy. By 2009, the ketogenic diet has become a well-established treatment supported by 2 randomized controlled studies demonstrating efficacy and a recently published international consensus guideline on its use. At no other time in the history of the ketogenic diet have basic and clinical scientists collaborated more to elucidate its mechanisms of action to ultimately enhance therapeutic strategies and to identify appropriate candidates. Given the advances in the field of ketogenic diet research, child neurologists should be reassured in their efforts to use the ketogenic diet and to consider adopting this treatment strategy sooner in the course of epilepsy treatment.

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