Epilepsia, **48**(1):31–42, 2007
Blackwell Publishing, Inc.

Critical Reviews

Clinical Aspects of the Ketogenic Diet

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Summary: The ketogenic diet remains a valuable therapeutic option for patients with intractable epilepsy. Clinical aspects of the diet's success may provide insights into epileptogenesis and anticonvulsant action. The diet's efficacy has been established primarily through large case series. The diet has been used successfully in patients with many different epilepsy syndromes in countries around the world. Potential adverse effects can be avoided with careful attention during the diet's initiation and maintenance phases. In the last decade, variations to the classical ketogenic diet have been utilized. Ketogenic diets now are being used for diseases other than epilepsy. This critical analysis of the diet should provide the impetus for further clinical and basic research into the diet's application and mechanisms of action. **Key Words:** Ketogenic diet—Epilepsy—Anticonvulsant—Intractable epilepsy.

"Intractable seizures continue to present a significant medical problem in the childhood age group, despite the availability of a great variety of anticonvulsant agents."

—Huttenlocher et al., 1971

"One who is confronted with the task of controlling seizures in a person with epilepsy grasps at any straw. When, some six or eight years ago, an osteopathic practitioner in Michigan stated that fasting would cure epilepsy, this seemed like a very frail straw. . .[but] in many patients there was freedom from seizures during fast."

—Lennox, 1928

WHY STUDY THE KETOGENIC DIET?

Huttenlocher's observations are as true today as they were 25 years ago, despite the introduction of more than 10 new anticonvulsants into the market (Huttenlocher et al., 1971). Newer medicines have provided an increased margin of safety, but there have been no major advances in efficacy over older agents. This emphasizes the importance of a different approach to how we think about anticonvulsant therapies. Although it might be considered by some to be a "last straw," as suggested by Lennox (Swink et al., 1997; Wheless et al., 2005), the ketogenic diet remains a useful part of the epileptologist's armamentarium. The ketogenic diet was introduced into clinical use in epilepsy differently than most medicines that were screened and selected using animal models, such as the maximal electroshock (MES) and pentylenetetrazol (PTZ) tests. However, recent history has taught that using these tests may be somewhat limiting in identifying drugs with novel mechanisms of anticonvulsant action (Rogawski, 2006). The most recent example of this is levetiracetam, which performed far better in a nonstandard test, the 6 Hz electrical stimulation model, than in classical models (e.g., MES or PTZ) (Barton et al., 2001). One potential (but unproven) explanation for this finding is that levetiracetam has a novel binding target, the SV2A receptor (Lynch et al., 2004). Given that the ketogenic diet was developed differently, studying the diet also may yield novel insights into seizures and epileptogenesis. Since its introduction as an anticonvulsant therapy, the ketogenic diet now is indicated specifically for patients with deficiencies in the GLUT-1 glucose transporter (where glucose cannot be transported into the cerebrospinal fluid for use by the brain) and pyruvate dehydrogenase (E1) deficiency (where ketone bodies can bypass the enzymatic defect). In this paper, we will describe some of the history of the ketogenic diet, its current clinical use, clinical research of the diet, and issues for future consideration.

HISTORY

It was noted early in history that fasting could be used in the treatment of epilepsy (Bailey et al., 2005). Descriptions of dietary restriction date back to the time of Hippocrates and are mentioned in the New Testament. High fat diets

Accepted October 23, 2006.
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doi:10.1111/j.1528-1167.2007.00914.x

also were considered nearly 140 years ago, but the first American use of the diet appears to have been near the beginning of the last century when a faith healer (Bernarr Macfadden) and an osteopathic physician (Dr. Hugh Conklin) advocated the use of fasting and prayer in a boy with seizures (Swink et al., 1997). As metabolism was better understood, the concept evolved that a high-fat diet could mimic the ketosis found during fasting. Around the same time, Wilder introduced the concept of a diet consisting of "ketogenic" and "antiketogenic" components for the treatment of epilepsy (Wilder, 1921; Swink et al., 1997). Groups in Minnesota, New York, and Maryland studied and used the diet in the intervening years, but its use appears to have declined with the introduction of diphenylhydantoin (phenytoin) in 1938 (Merritt and Putnam, 1938). About 12 years ago, the treatment of a child at the Johns Hopkins Hospital precipitated the most recent interest in the ketogenic diet (Freeman et al., 2006).

DESCRIPTION OF THE KETOGENIC DIET

The ketogenic diet is high in fat content and low in carbohydrate and protein content. Although it is a "ketogenic diet," one nutrient class (carbohydrates) is depleted, while providing an alternative fuel source for the brain with another substrate (ketones), which may be anticonvulsant. Dietary protein also is decreased slightly in the ketogenic diet. The typical ratio of fats to carbohydrates and protein (in terms of grams) is 3:1 or 4:1, although lower ratios are used successfully in other parts of the world, such as Asia, where rice is a major dietary staple (Kossoff and McGrogan, 2005). During the ketogenic diet, a number of parameters are followed, similar to patients taking medication, including the patient's seizure control and lack of side effects. Given the dietary nature of the ketogenic diet, however, other parameters also are critical, including adequate growth. Adherence to the regimen can be followed with a simple laboratory measurement that can be done at home, ketonuria.

The Johns Hopkins Hospital (JHH) protocol

The general protocol followed at our institution has evolved over time, as new advances have been made in how the diet is administered (Table 1). Key members of the team managing the patient include physicians, nutritionists familiar with the diet, nursing staff, and, most importantly, patients and their families. Prior to introducing the ketogenic diet, patients are screened by history and exam (and supporting laboratory studies, if indicated) for metabolic disorders that may affect their ability to generate adequate amounts of ketones. For example, defects in fatty acid oxidation generally are contraindications to starting the ketogenic diet. Absolute contraindications to the ketogenic diet include pyruvate carboxylase deficiency and porphyria. Relative contraindications include certain mitochondrial cytopathies (although this recommendation has been liberalized over time based on case series and experience in our center; in particular, it may be useful in some Complex I deficiencies), and known carnitine deficiencies (Wilder, 1921; Sinha and Kossoff, 2005).

Prior to admission, a complete dietary history is obtained, and the dietician and physician determine the ketogenic ratio that will be used, and the caloric and fluid contents of the patient's diet. Carbohydrate intake is decreased for about 24 h, duration based on dietary history. Once admitted, patients continue fasting (fluids are still given) with blood glucose checks every 6 h. Glucose levels as low as 25–40 mg/dL do not need treatment unless the patient becomes symptomatic (e.g., extreme lethargy, severe emesis). On the first day of feeding, the patient is given 1/3 of the planned total caloric intake (as an "eggnog"); on the second day, 2/3 of the total calories are administered, and on day 3, the full (previously calculated) caloric intake is administered. The total amount of calories in the diet is based on anthropometric measurements, dietary intake prior to the diet's initiation, and size-appropriate recommendations for fluid and calories. The typical outpatient dietary regimen includes three meals and two snacks during a 24-h period (Table 2). Multivitamins are given to all patients, as the ketogenic diet is not nutritionally complete (i.e., it is low in calcium and certain micronutrients, such as zinc, selenium, and copper). Citrate is also given to patients with a family history of nephrolithiasis or those with a high urine calcium:creatinine ratio, as the risk for nephrolithiasis is increased during the ketogenic diet (see below). During the diet's initiation, blood glucose, urine ketones, and vital signs are followed. Classes on nutrition, diet management, menu preparation, avoidance of extraneous sugar intake (e.g., in medications), and sick day management are given by the staff. Special attention is paid to patients on carbonic anhydrase inhibitors (e.g., topiramate, zonisamide, acetazolamide), given the theoretical risk of nephrolithiasis. In practice, these medicines have not been shown to increase the risk of kidney stones, however (Kossoff et al., 2002a).

The outpatient phase of the ketogenic diet consists of routine clinic visits (3, 6, 12, 18, and 24 months after starting the diet) with the staff and laboratory measurements, along with frequent contact with the nutritionist. Typically, medications are tapered once efficacy of the diet has been established (usually within 3–6 months of diet initiation), but can be tapered earlier if the patient has significant medication side effects (Kossoff et al., 2004). Families are taught to check urine ketones and monitor for other illnesses if there is an increase in seizure frequency. At times, a brief fast or change in short-acting medication may provide transitory relief from increased seizures. Changes to the dietary regimen usually are made only if there is a sustained increase in seizure frequency without an obvious precipitant (e.g., accidental ingestion of sugars such as maltodextrin, sorbitol, fructose, and others) or if

TABLE 1. *Typical ketogenic diet initiation regimen*

Before diet
Nutrition history obtained
Minimize carbohydrate intake for 1 day
Fasting begins after dinner the evening prior to admission
Day 1
Admission to the hospital
Conversion to carbohydrate-free medications
Basic laboratory results obtained if not done previously (metabolic profile, urine calcium, urine creatinine, fasting lipid profile, antiepileptic drug levels)
Check fingerstick glucose every 6 hr; if <40 mg/dL, check every 2 hr
If symptomatic, or glucose <25 mg/dl, give 30 ml orange juice, measure blood glucose again
Parents begin classes
At dinner, one third of the calculated ketogenic meal given as "eggnog" (e.g., if the full meal is calculated as 150 ml, give 50 ml at this meal)
Blood glucose checks discontinued after dinner
Day 2
At breakfast and lunch, one-third of the calculated ketogenic meal given as "eggnog"
Symptomatic ketosis (e.g., nausea, vomiting) can be relieved with small quantities of orange juice
Parent classes continue
At dinner, two-thirds of the calculated ketogenic meal given as "eggnog"
Day 3
At breakfast and lunch, two-thirds of the calculated ketogenic meal given as "eggnog"
Parent classes conclude
At dinner, the first full ketogenic meal is given (not "eggnog")
Day 4
After breakfast (full ketogenic meal), the patient is discharged to home
Prescriptions written for carbohydrate-free medications, urine ketone test strips, a sugar-free, fat-soluble multivitamin and calcium supplements, citrate salts (if indicated)
Clinic follow-up appointment arranged

the child is losing weight (Sinha and Kossoff, 2005). If the child is gaining weight but has excellent seizure control, we would not change the diet. Variables such as ketogenic ratio, caloric intake, and fluids can all be manipulated to achieve better seizure control or improved growth. The diet is discontinued for the following reasons: certain toxicities (see below), seizure freedom for 2 yr, inability to maintain the regimen, lack of efficacy, and patient or family requests. If it is discontinued for seizure freedom, the diet can be tapered by gradual change of the ketogenic ratio (i.e., 4:1–3:1, etc.) through a variety of dietary strategies (Sinha and Kossoff, 2005).

Modifications to the JHH protocol

A number of modifications to the classical JHH protocol have been evaluated. One fundamental question is whether fasting is necessary before the diet is introduced. Three studies examined this question as proof-of-concept case series demonstrating feasibility of not performing a fast (Wirrell et al., 2002; Kim et al., 2004; Vaisleib et al., 2004). One of these studies also found that outpatient initiation of the diet did not lead to differences in long-term seizure control (Vaisleib et al., 2004). Time to ketonuria and incidence of hypoglycemia was not different in one study, but moderate dehydration was more common in historical controls on a conventional ketogenic diet initiated with fluid restriction (Kinsman et al., 1992; Freeman et al., 1998; Kim et al., 2004). A prospective, randomized study showed that there was no difference in efficacy at 3 months between the fasting and nonfasting groups; children in the nonfasting group were less likely to lose weight, become hypoglycemic, require treatment for acidosis, or become dehydrated (Bergqvist et al., 2005). Ketosis was achieved sooner is fasting patients, but all were ketotic within 5 days. It should be noted that hypoglycemia was treated at a higher glucose level ($\leq$45) than that typically done in the JHH protocol, raising a question about differences in methodology of diet initiation between this cohort and the JHH group. The ketogenic diet regimen also was introduced in a different fashion than at Johns Hopkins, with full calories being administered each day and the ratio varying with each day (i.e., on day 1 of feeding, a 2:1 ratio was administered; on day 2 of feeding, a 3:1 ratio was administered, etc.). Clinical researchers of the diet continue to advocate hospitalization for diet initiation because even children who are not fasted may have metabolic problems precipitated by this major change in nutrition. One distinct advantage to the fasting phase is that it gives physicians and families the chance to observe the patient's reaction in a controlled environment, and a brief fast may

TABLE 2. *Sample menu for one day on the ketogenic diet*

Breakfast
Breakfast quiche with bacon
Lunch
Belgian salad with avocados, pineapple, and pecans
Dinner
Sausage, potato, sauerkraut
Creamy milkshake
Snacks
Cheesecake with blueberries
(total: 1000 calories/ 3.8:1 ratio)
Total cost for the day: $2.94

be a therapeutic strategy to improve seizure control as an outpatient.

The quality of the fats used in the ketogenic diet has been the subject of study. The classical ketogenic diet uses long-chain triglycerides (LCT). Medium-chain triglycerides (MCT) are more ketogenic than LCTs, as octanoic and decanoic acids are more easily transported into the cell (Huttenlocher, 1976). Since it is more ketogenic, the MCT ketogenic diet (MCT-KD) allows for a lower overall fat content and subsequent greater inclusion of protein and carbohydrate in the daily intake (Sinha and Kossoff, 2005). Clinically, there does not appear to be a difference in efficacy between the MCT and the LCT diets (Huttenlocher et al., 1971; Schwartz et al., 1989a). Patients on the MCT diet are more likely to experience abdominal bloating and diarrhea than those on the LCT diet, which is believed by some to be less palatable than the MCT diet. Patients on the LCT diet are more prone to constipation than those consuming an MCT diet. Another diet was developed at the John Radcliffe Infirmary (Schwartz et al., 1989a). This diet incorporates some of the palatability of the MCT diet into the LCT diet, although in this study, which was not an intent-to-treat analysis, there was no change in efficacy compared to either of the other diets (Schwartz et al., 1989a). Other options for using the diet in patients fed through a gastrostomy tube or in infants include prescribed formulations of the Ross Carbohydrate-Free Formula, Ross Columbus, OH, U.S.A. with Ross polycose (Ross) and microlipids; another liquid form is Keto-Cal (Nutricia North America, Gaithersburg, MD, U.S.A.). The availability of these formulas for infants, particularly those with gastrostomy tubes, makes palatability less of an obstacle in this patient population (Sinha and Kossoff, 2005).

CLINICAL STUDIES OF THE KETOGENIC DIET

Methodological issues

Prior to reviewing the clinical literature on the ketogenic diet, certain methodological issues should be addressed. The first issue to address is studies assessing efficacy. Most series published to date have been small series of patients with diverse pathologies, making direct comparisons between groups difficult. Different investigators have looked at the diet's success at different time points (chosen primarily for convenience, not because the time points have been validated as clinically or statistically meaningful). When time points have been chosen, most studies have not specified whether the outcome was for a given interval (e.g., for the week prior to the 3 month postdiet visit versus the last month at the 6 month postdiet visit). The diet is subject to the same problems with seizure recall and seizure calendars as studies of any medical or surgical intervention for epilepsy. It is difficult to assess the effect of an intervention versus the natural history of the patient's epilepsy, although some studies of the diet (both retrospective and prospective) have looked at 2–6 yr of follow-up. In other words, consistency of the changes over time has not been studied adequately. Studies of the diet frequently only look at what the parents believe is the 'most important' seizure to eliminate, so we do not have an accurate representation of how patients with multiple seizure types fare with each one individually. Each of the diets noted above has been studied in some detail, although direct multicultural comparisons of the diet in its global application have not been done (Kossoff and McGrogan, 2005). As an example, the ketogenic diet in Asia can have a slightly lower ketogenic ratio (given the increased ketogenicity of certain foods) and still be effective. Its successful implementation, however, speaks to its generalizability and the dedication of the staff caring for these patients.

The second issue is studies assessing why the ketogenic diet appears to work, a more difficult question. It is important to note that changes seen in patients consuming a ketogenic diet may not all be responsible for the diet's anticonvulsant effects (i.e., some of these changes may be epiphenomena). Given that the ketogenic diet was designed to mimic the fasting state, some studies of the diet's anticonvulsant mechanism have looked at physiological changes in humans based on subjects who fasted only for brief periods of time. The ketogenic diet is a chronic therapy, however. Acute alterations during fasting may not reflect accurately the changes in patients chronically fed a high-fat, carbohydrate-depleted diet (R. Veech, personal communication, 2006). The method of measuring these changes also varies between studies, each with its own limitations. As an example, various methods of measuring ketone levels have been published, including urine, serum, breath, and brain magnetic resonance spectroscopy, with no clear indication of which one best reflects clinical seizure control (if, in fact, any do).

Does it work?

Efficacy of the ketogenic diet was reported to be high in early studies, with 60% of patients enjoying total freedom from seizures, and another 35% showing greater than a 50% decrease in seizure frequency (Peterman, 1925). A retrospective analysis of the Hopkins cohort prior to the most recent resurgence of interest in the diet showed that 29% of patients had nearly complete control of their seizures (Kinsman et al., 1992). Retrospective studies were not generally reported in an intent-to-treat analysis, particularly important when patients were known to discontinue the intervention. Discrepancies between retrospective studies (which tended to be less current) and prospective studies may be due to the fact that older studies did not always account for patients who stopped the diet, and the fact that children in more recent studies have had an exposure to a wider spectrum of anticonvulsant

agents, with the implication that they may have been more refractory to standard therapy (Vining, 1999).

The largest single-institution intention-to-treat prospective study (150 patients at the Johns Hopkins Hospital) demonstrated at 3 months (with 125 patients remaining on protocol) that 3% of patients were free from seizures, 31% had a greater than 90% reduction in seizure frequency, and 26% had a 50–90% reduction in seizures (Freeman et al., 1998). After 12 months (83 patients remaining on protocol), 7% were free from seizures, 20% had a greater than 90% reduction in seizure frequency, and 23% had a 50–90% reduction in seizures. Results from a multicenter study (using the same dietary protocol) were within 5% of those from the Hopkins study, thus demonstrating the adaptability and transportability of the diet (Vining et al., 1998).

Meta-analyses of the ketogenic diet have summarized the efficacy of the ketogenic diet, although they include both prospective and retrospective studies with the caveats noted previously. One study performed for an insurance group (Blue Cross/Blue Shield) showed complete cessation of all seizures in 16% of children, greater than 90% reduction in seizures in 32%, and greater than 50% reduction in seizures in 56% (Lefevre and Aronson, 2000). Another analysis using different methodology showed an odds ratio of 2.25 (95% confidence interval 1.69–2.98) for success in decreasing seizures by $\geq$50% (Henderson et al., 2006). Given the lack of randomized controlled trials (RCT), a Cochrane database review concluded the ketogenic diet is a 'possible option' in the treatment of intractable epilepsy (Levy and Cooper, 2003). Similar to the ketogenic diet, a recent evidence-based analysis of efficacy and effectiveness highlighted the lack of evidence for many antiepileptic agents used today (Glauser et al., 2006). The nature of the diet precludes blinding to certain features of the diet, although a forthcoming study from Johns Hopkins used randomized administration of glucose and a nonglucose sweetener, saccharin. Another study in progress at the Great Ormond Street Hospital randomized patients to the MCT-KD or the classical ketogenic diet, with further randomization to start the diet after a nontreatment period lasting either four or 16 weeks, thus generating a controlled parallel-group design (Neal et al., 2004). A true placebo-controlled RCT with adequate duration of therapy is difficult to design, given the nutritional interventions involved and the risk of seizures.

Follow-up studies done 3–6 yr after the diet was initiated showed that nearly 27% of the prospective Hopkins cohort enjoyed a seizure reduction greater than 90%, with nearly 20% of patients (of the original 150) being off medication (Hemingway et al., 2001). Although this is cited as possible evidence for an antiepileptogenic effect of the diet (Gasior et al., 2006), a small but substantial number of patients (32%) who have only a partial response to the ketogenic diet may experience a significant decrease in seizure frequency eventually (Marsh et al., 2006). This raises the interesting questions of whether we know enough about the natural history of how truly intractable 'medically intractable' epilepsy is in children or whether even a partial response to the ketogenic diet might serve as a marker for later improvement in seizure control (Marsh et al., 2006).

One factor that has not been studied adequately is whether the diet prescribed today is truly comparable to the way it was prescribed in past years. In the first half of the 20th century, the diet was initiated with a prolonged fast, with children required to lose 5–10% of their body weight and caloric intake on the diet was restricted considerably. Current sensitivity to the child's well-being and growth has made the initiation and maintenance phases of the diet less stringent. Thus, comparisons of efficacy between early studies of the diet and those done more recently may not be entirely valid.

Does the ketogenic diet work better in certain patients?

The multicenter study of the ketogenic diet showed no relationship between outcome and age, sex, principal seizure type, or EEG (Vining et al., 1998). This study also demonstrated implementation of the diet in a variety of settings (e.g., academic or private practices), although there was no formal comparison of the various practice locations because the number of patients from each center was too small. The prospective Hopkins study confirmed the lack of differences in seizure control based on age, sex, seizure type, or seizure frequency (Freeman et al., 1998).

The ketogenic diet has been used in patients with a variety of types of seizures and epilepsy syndromes, including Lennox-Gastaut syndrome (Freeman and Vining, 1999), infantile spasms (Nordli et al., 2001; Kossoff et al., 2002b; Eun et al., 2006), myoclonic-astatic epilepsy (Oguni et al., 2002; Caraballo et al., 2006a), Dravet syndrome (Caraballo et al., 2005; Fejerman et al., 2005) (where there is a suggestion that earlier diet intervention leads to better outcomes) (Caraballo et al., 2006b), tuberous sclerosis (Kossoff et al., 2005; Coppola et al., 2006), Landau-Kleffner syndrome (Bergqvuist et al., 1999) and Rett syndrome (Haas et al., 1986). The only seizure type that might not have an early, dramatic response (defined as patients who became seizure free within 2 weeks of their ketogenic diet admission and remained seizure free afterward for $\geq$6 months) is complex partial seizures, although many patients with partial-onset seizures have excellent results (similar in one series to those with generalized epilepsy), and some eventually become seizure-free (Maydell et al., 2001; Than et al., 2005). The ketogenic diet did not stop disease progression in patients with Lafora body disease (Cardinali et al., 2006).

The ketogenic diet is used typically after a patient has been failed by numerous medications; by current

definitions, these patients have intractable epilepsy. A retrospective study showed that the diet has similar efficacy when used after zero or one medication has been tried (i.e., before intractability) (Rubenstein et al., 2005). This raises the important question about when the diet might be best used in the course of a patient's epilepsy. The optimal timing of when to use the diet (i.e., early vs. late) has not been studied prospectively. The optimal duration of how long patients should be treated (e.g., the standard 2 yr vs. shorter time periods) also has not been established.

Despite its use primarily in children, the ketogenic diet has been used successfully in adults with epilepsy, demonstrating that adults with partial epilepsy can achieve ketosis and seizure control (Sirven et al., 1999). This is in contrast to earlier studies suggesting greater efficacy of a ketogenic diet in younger (rather than older) children and adults (Huttenlocher et al., 1971; Schwartz et al., 1989a). Adolescent patients adhere successfully to the regimen as well as younger children (Mady et al., 2003). Considering illnesses other than epilepsy, adults with Parkinson disease can adhere to the regimen, at least under research conditions (Vanitallie et al., 2005). Infants can also be treated successfully with the ketogenic diet (Nordli et al., 2001; Kossoff et al., 2002b).

In summary, the ketogenic diet works in patients of all ages and seizure types in a variety of settings. Given the methodological caveats mentioned earlier, it does not appear to work better in any particular type of patient. If a patient has been intractable to medication therapy and the burden of seizures or medication side effects is significant (i.e., interferes with normal function), the ketogenic diet should be considered. It is not a benign therapy, but it should be considered if the benefit/risk ratio is favorable. It is not known whether there is an optimal time in the course of a patient's epilepsy to introduce the diet.

INDICATORS OF EFFICACY

Aspects of the diet that are crucial to efficacy would be useful to know in order to optimize outcomes while minimizing the impact these diets have on patients and their families (Vining, 1999). Variables that can be adjusted include calories, ratio of fat to carbohydrate, quality of fats or carbohydrates, schedules during seizure exacerbations, and timing of meals (Vining, 1999).

The most common way to measure adherence to the ketogenic diet regimen is urine ketones (specifically, β-hydroxybutyrate, and acetoacetate), an easy and relatively cost-effective indicator of ketosis. In the classical ketogenic diet studies have failed to support a correlation between anticonvulsant efficacy and levels of the major ketone body β-hydroxybutyrate in the urine (Ross et al., 1985), and serum (Frasier et al., 2003). Urine ketones measured on dipsticks at the highest level can be consistent with serum β-hydroxybutyrate levels anywhere from 2 to 12 mmol/L (Gilbert et al., 2000). Serum levels might correlate with an anticonvulsant effect somewhat better than urine (Gilbert et al., 2000). One study of the medium chain triglyceride version of the diet (MCT-KD) suggested a threshold effect, wherein a certain level of plasma β-hydroxybutyrate and acetoacetate (the other major ketone body produced during the ketogenic diet and starvation) might be necessary for an adequate anticonvulsant effect (Huttenlocher, 1976). However, another study comparing the classical MCT-KD, and a modified MCT-KD (the Radcliffe Infirmary diet) failed to show a correlation between ketone levels and seizure control (Schwartz et al., 1989b). Ketonemia and ketonuria (specifically measuring β-hydroxybutyrate and acetoacetate) therefore, probably serve as better indicators of adherence than efficacy. The suggestion of a threshold effect of these ketone bodies is suggested by data from some studies, but ketonuria probably serves as a surrogate (rather than a direct) marker of adherence, rather than efficacy. Degree of ketonuria does not correlate with seizure control on the Atkins diet (Kossoff et al., 2006).

Acetone is the third major ketone body formed in patients consuming a ketogenic diet. It is formed by the spontaneous decomposition of acetoacetate, and is highly volatile, making its measurement a challenge. Nonetheless, acetone possesses anticonvulsant properties, so its measurement might serve as an indicator of efficacy (Likhodii et al., 2003). Using technology based on breathalyzers for detecting alcohol levels in drivers, breath acetone correlated with plasma levels of all three ketone bodies in patients with epilepsy on the ketogenic diet, although there was no correlation with seizure activity (Musa-Veloso et al., 2006). In a brain magnetic resonance spectroscopy study, not all patients whose seizures were controlled had elevated brain levels of acetone (Seymour et al., 1999). Thus far, it does not appear that acetone levels correlate with levels of seizure control.

One tool readily available in neurology centers is EEG. Studies have failed to correlate consistent EEG changes with seizure protection in most patients consuming the ketogenic diet (Huttenlocher et al., 1971; Schwartz et al., 1989a; Vining et al., 1998; Fraser et al., 2003). Data from one study suggested EEG correlation with efficacy might be dependent on seizure type (Janaki et al., 1976; Vining, 1999). Early improvements in EEG were not sustained in another study of children with atypical absence epilepsy, despite clinical improvements in two-thirds of the patients (Ross et al., 1985). One major exception to this notion is that the EEG pattern of hypsarrhythmia may improve in patients with infantile spasms on the ketogenic diet; whether this is a direct effect of the diet or part of the natural history of the disorder remains to be determined (Kossoff et al., 2002b).

In summary, none of the clinical or laboratory markers studied thus far have correlated with efficacy. From a

practical perspective, ketonuria remains the most noninvasive and cost-effective means of documenting adherence to the regimen. In this high-tech age, the best marker of efficacy remains the clinical history.

NATURAL HISTORY AND DURATION OF THERAPY

Some patients may experience a dramatic decrease in seizure frequency during the initial fasting phase; not all these patients, however, enjoy long-term seizure freedom (Freeman and Vining, 1999). Others do not have this initial dramatic effect, but may still enjoy long-term freedom from seizures. The multicenter and prospective Hopkins studies showed that patients who enjoyed a greater than 50% decrease in seizures were statistically more likely to stay on the diet for longer than those whose reduction in seizures was less than 50% (Freeman et al., 1998; Vining et al., 1998). The prospective Hopkins study demonstrated that the most common reasons for stopping the diet were either lack of efficacy or the diet being perceived as too restrictive, findings that were confirmed in a 3–6 yr follow-up study (Freeman et al., 1998; Hemingway et al., 2001).

SIDE EFFECTS

The ketogenic diet is not a benign therapy, being associated with a number of side effects. Some effects are very predictable, preventable, and potentially treatable, such as dehydration and hypoglycemia (Ballaban-Gil, et al., 1998; Vining, 1999; Kang et al., 2004). Most patients have a mild acidosis at baseline. Other effects have been the subjects of isolated case reports, so while serving a cautionary function, their consistent relationship to the ketogenic diet is unknown (e.g., cardiomyopathy, renal tubular acidosis). An example of a consistently noted side effect is nephrolithiasis, seen in 6% of patients on the ketogenic diet (Furth et al., 2000). Effects of the diet, especially hypocitruria, hypercalciuria, and aciduria, contribute to stone formation (most commonly consisting of urate or calcium). All patients now are screened for a family history of nephrolithiasis and for hypercalciuria (before starting the diet) with a urine calcium/creatinine ratio (>0.2 is considered abnormal). Patients with an elevated calcium/creatinine ratio, hematuria, or those taking carbonic anhydrase inhibitors (e.g., topiramate, zonisamide, or acetazolamide) with a concomitant personal or family history of nephrolithiasis are prescribed oral citrate salts as prophylaxis (e.g., Polycitra K, Mc Neil, San Bruno, CA, U.S.A.) (Kossoff et al., 2002a). Nephrolithiasis is treated by increasing fluid intake, alkalinization of urine, and discontinuation of carbonic anhydrase inhibitors; depending on the patient's symptoms, timely referral is made to Urology.

Table 3 lists other side effects by organ system, some of which are based on isolated case reports. Anticipated effects, such as lipid abnormalities, may not have short-term effects, but the relevance of this finding (in children typically exposed to the diet for only 2 yr) is unknown over the lifetime of a patient (Kwiterovich et al., 2003). Growth (height and weight) may be impaired, an effect most noticed in younger children (Vining et al., 2002; Liu et al., 2003).

TABLE 3. *Side effects of the ketogenic diet*

Metabolic	Renal
Acidosis	Symptomatic nephrolithiasis (6%)
Weight loss	*Fanconi renal tubular acidosis*
Inadequate growth	Dehydration
Rapid ketosis/acidosis	Neurological
Hyperlipidemia	*Basal ganglia changes*
Vitamin, trace element deficiency	*Coma, obtundation*
Hypoglycemia	*Optic neuropathy (thiamine deficiency)*
Hyperuricemia	Hematological
Low Na, Mg	*Anemia*
GI	Easy bruising
Nausea/emesis (initiation)	*Leukopenia*
Constipation (classic KD)	Orthopedic
Diarrhea (MCT-KD)	*Fractures*
Worsening GERD	Infectious disease
Acute pancreatitis	*Susceptibility to infection*
Hypoproteinemia	Unknowns
Cardiac	Bone
Prolonged QT syndrome	Muscle
Cardiomyopathy	Liver

Note: Italics indicate case reports.

Put into perspective, the most common side effects of the diet are routinely monitored during follow-up clinic visits (e.g., at 3 and 6 months) that include laboratory work (serum chemistries, blood counts, fasting lipids, urinalysis, and urine calcium/creatinine ratio). Growth is monitored closely. Vitamin and mineral supplementation is provided to prevent known deficiencies. Gastrointestinal complaints can be treated with fluid intake, dietary adjustments, and laxatives (Sinha and Kossoff, 2005). During the diet initiation admission, families are counseled about signs and symptoms of possible side effects.

Of great concern is effects that may not have an immediate manifestation, but could have implications for the patients' long-term health. We do not know if there is a 'vulnerable period' of exposure to the ketogenic diet for a limited (or extended) time. This could have implications for the health of the vasculature (e.g., atherosclerosis), bone (e.g., osteoporosis), liver (with its major role in ketogenesis), and muscle (a major storehouse of mitochondria in the body).

OTHER ANTICONVULSANT DIETS

The tremendous commitment made by patients and their families to adhere to the ketogenic diet regimen stimulated interest in less restrictive dietary regimens for treating intractable epilepsy. Viewed along a continuum, the dietary therapy of epilepsy has evolved from fasting to the ketogenic diet to newer interventions, such as the Atkins diet and the low glycemic index treatment (LGIT);

perhaps an easier intervention (even in pill form) is the next major advance in this area. A modified Atkins diet allows greater carbohydrate and protein intake than the ketogenic diet and now has been shown to be efficacious in adults and children (Kossoff, et al., 2003, 2006). Another regimen, the LGIT, addressed the quality of carbohydrate consumed; foods that produce a greater rise in serum glucose (e.g., jelly beans) are avoided in this diet, replaced by those producing a comparatively lower rise in serum glucose (e.g., soybeans). The LGIT also showed efficacy in a case series, although the details of how the diet is prescribed are not widely known (Pfeifer and Thiele, 2005). These results suggest that some restriction of carbohydrates may be sufficient to produce an anticonvulsant effect. Animal data suggest that caloric restriction may also play a role in seizure protection (Bough et al., 2003). These data emphasize the importance of the low carbohydrate component of the ketogenic diet. The ketogenic diet is also (and better known for being) high in fat content. The role played by the high-fat component of the ketogenic diet is somewhat unclear, as the quality of the fat component can either consist of LCT or MCT. LCT diets consist of predominantly saturated or unsaturated fats, although polyunsaturated fats appear to more ketogenic than saturated fats (Fuehrlein et al., 2004; Sankar, 2004). The MCT diet can have a corn oil substitute and be used successfully in epilepsy (Woody et al., 1988). Additionally, there are data showing serum levels of arachidonate, a polyunsaturated fatty acid, correlate with seizure control (Fraser et al., 2003).

A totally different approach to the dietary therapy of epilepsy was proposed in the 1980s. An oligoantigenic diet was effective in a small number of patients with both migraines and epilepsy, but not those with epilepsy alone (Egger et al., 1989). The diet consisted of limited exposure to different groups of foods (e.g., lamb and chicken were the only two meats allowed for the first 4 weeks of the diet; bananas and apples were the only fruits allowed during the same time). The diet was not ketogenic. Patients had either partial or generalized epilepsy syndromes (including Lennox-Gastaut syndrome and myoclonic-astatic seizures). After rechallenge with specific foods, some patients experienced worsening seizures. The implications of treatment with an oligoantigenic diet are beyond the scope of this paper, but this work makes an interesting comment on the dietary therapy of epilepsy. Aspartame ingestion did not appear to influence seizure activity in one study, although it worsened spike-wave discharges in another one (Camfield et al., 1992; Rowan et al., 1995).

FACTORS OTHER THAN SEIZURE CONTROL

Cognition and alertness can improve while patients are on the ketogenic diet (Kinsman et al., 1992; Nordli et al., 2001). Whether this is due to improvement in seizure control, decreased medication, or a nonspecific effect of the diet (or a combination of all the above) is uncertain. Developmental quotients, attention, and social function were also noted to improve in a prospective study at Johns Hopkins (Pulsifer et al., 2001). In a study of parental expectations, cognitive improvement ranked third (behind seizure control and medication reduction), with 90% mentioning improvements in cognition or alertness as factors they were seeking prior to initiating the diet (Farasat et al., 2006). Perceived cognitive improvement correlated positively with duration of staying on the diet. Particularly important in these times of increased scrutiny of rising costs of medical care, use of the ketogenic diet can decrease overall costs of care and medications (Gilbert et al., 1999; Mandel et al., 2002), although there is a cost incurred for the initial hospitalization. The primary cost savings comes from the decreased use of medications and improved seizure control; patients need to eat anyway, and ketogenic foods might actually be less expensive than a normal diet (EPGV, unpublished data; Table 2).

CLINICAL DATA ON THE ANTISEIZURE EFFECTS OF THE KETOGENIC DIET

The mechanism(s) underlying the beneficial effects of the ketogenic diet on seizures remain a mystery. A discussion on the basic science of the ketogenic diet is presented in a companion article (Bough and Rho, 2007). Some of the original hypotheses of how the ketogenic diet works, however, were generated from patient data. Original hypotheses about the diet's anticonvulsant mechanism of action that have been subsequently disproved in clinical studies include systemic acidosis (Huttenlocher, 1976; Ross et al., 1985), electrolyte changes (Chesney et al., 1999), and hypoglycemia (Ross et al., 1985; Fraser et al., 2003). Discussions on the roles of ketone bodies and polyunsaturated fatty acids are included in other sections of this review. Neurotransmitter levels may change during the ketogenic diet. One brain MR spectroscopy study of GABA, the major inhibitory neurotransmitter in the human central nervous system, showed mixed results, with levels increasing after the diet was introduced in two patients, but decreasing after the diet was introduced in another patient (Wang et al., 2003). In a study of CSF amino acid and neurotransmitter levels in children on the ketogenic diet, GABA levels were higher in children who responded to the diet (compared to those who did not respond), although those who responded best had higher GABA levels at baseline and during the diet (Dahlin et al., 2005). Studies of plasma and CSF amino acids have shown inconsistent results (Schwartz et al., 1989b; Dahlin et al., 2005). Although these studies suggest a role for GABA in the diet's anticonvulsant effects, it is important to note that patients who respond to the ketogenic diet typically have not benefited from medicines that have

effects on GABA synthesis, receptors, or metabolism, thus weakening a GABAergic hypothesis. MR spectroscopy studies have also suggested an overall improvement in cerebral energy state during the ketogenic diet (indicated by ATP levels), although the relevance of this finding to the anticonvulsant mechanism of the diet in humans is unknown (Pan et al., 1999). In summary, clinical studies have suggested two potential mechanisms for the anticonvulsant efficacy of the ketogenic diet: arachidonate levels and CSF GABA levels. The relative importance and generalizability of these findings remain to be determined.

OTHER APPLICATIONS OF THE KETOGENIC DIET

For various reasons, the ketogenic diet has been tried in conditions other than epilepsy. In Parkinson's disease, the ketogenic diet is believed to bypass the involvement of mitochondrial complex I (implicated in the pathogenesis in some forms of this disease), but beneficial effects in a small case series need to be controlled for potential dietary alterations with an impact on the absorption of levodopa, a medication used to treat the disease (VanItallie et al., 2005; Jabre and Bejjani, 2006). The bypass of the initial steps (and enzyme defects) in glycolysis forms the basis for the diet's utility in pyruvate dehydrogenase deficiency, as noted previously. Similarly, the diet may be useful in infantile phosphofructokinase deficiency (Swoboda, et al., 1997) and glycogenosis type V (McArdle disease) (Busch et al., 2005). Case reports have described successful use of the ketogenic diet in two children with astrocytomas, with the belief that tumor cells are more dependent on glycolysis than normal cells, resulting in tumor cell death (Nebeling et al., 1995; Seyfried and Mukherjee, 2005).

Other illnesses that have been reported in case series to benefit from the ketogenic diet are migraine headaches (Strahlman, 2006), autism (Evangeliou, et al., 2003), and depression (Murphy et al., 2004). Patients with illnesses involving known or purported derangements in glucose metabolism, including type 2 diabetes mellitus and polycystic ovary syndrome, have been shown in case series to benefit from the ketogenic diet (Mavropoulos et al., 2005; Yancy et al., 2005). Paradoxically, patients with hypercholesterolemia may also benefit from the ketogenic diet (Dashit et al., 2006). The Atkins diet, in addition to its use in weight loss, may have a beneficial effect on patients with narcolepsy (Husain et al., 2004). Adults with rheumatoid arthritis did not appear to benefit from an exposure to the ketogenic diet for 7 days in terms of clinical signs or inflammatory markers (Fraser et al., 2000), although the authors demonstrated improvement in these findings after a 7-day fast in prior work (Fraser et al., 1999). Animal models of Alzheimer's disease and amyotrophic lateral sclerosis have shown benefit from the ketogenic diet (Van der Auwera, 2005; Zhao et al., 2006).

FUTURE DIRECTIONS

The ketogenic diet's efficacy in treating intractable epilepsy raises questions that may impact our knowledge of epileptogenesis. Is the ketogenic diet anticonvulsant, antiepileptogenic, or both? What is the relative importance of calorie restriction, ketosis, and glucose utilization? Considering disorders other than epilepsy, do other properties of the ketogenic diet have their own uses (e.g., neuroprotection)?

Current trends in clinical research of the ketogenic diet include modifications to the diet (e.g., quality of the individual components of the diet, especially unsaturated vs. saturated fats and different types of carbohydrates), identification of groups of patients in whom the ketogenic diet works best, combinations of the diet with other modalities, sequencing of when the diet might be best employed (e.g., earlier rather than later in the course of epilepsy), how to "rescue" patients who have good initial seizure control, then (for unknown reasons) seem to lose its protective effects, reasons for why seizure control is lost after a period of success and stability on the diet, management of side effects, and applying the diet in illnesses other than epilepsy.

Proposed mechanisms for the diet's anticonvulsant and antiepileptic effects should take into account certain clinical observations, including the prevention of seizures with different diets (e.g., ketogenic diet, modified Atkins diet, and LGIT), rapid onset of effect during fasting for some patients (but delayed for others), and an apparent long-term protection from epilepsy (or even cure) in selected patients.

CONCLUSIONS

The ketogenic diet is a useful therapy for patients with intractable epilepsy, including some of the catastrophic epilepsies in infancy and childhood. Its efficacy is at the very least, comparable to anticonvulsant medications (Freeman et al., 2006). The ketogenic diet can be used in patients of all ages. As the ketogenic diet is applied in illnesses other than epilepsy (many of which occur in adulthood), physicians will turn to epileptologists familiar with its use for advice and guidance. Modifications to the classical ketogenic diet may make it more practical for use in patients with these other illnesses. Given its likely unique mechanism(s) of action, study of the ketogenic diet may also provide insights into epileptogenesis. Although it has been in clinical use in this country for nearly 90 yr, we appear to be on the cusp of another surge in the study of the clinical applications and clinical insights related to its use. This 'last straw' seems to have stood the test of time, particularly in the face of all the new medicines available (Lennox, 1928; Huttenlocher et al., 1971).

Acknowledgments: This work was supported by the General Clinical Research Center, M01-RR-00052 from the National

Center For Research Resources-National Institutes of Health and the Epilepsy Foundation through the generous support of Pfizer, Inc. (ALH).

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