

SPECIAL REPORT

Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group

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SUMMARY

The ketogenic diet (KD) is an established, effective nonpharmacologic treatment for intractable childhood epilepsy. The KD is provided differently throughout the world, with occasionally significant variations in its administration. There exists a need for more standardized protocols and management recommendations for clinical and research use. In December 2006, The Charlie Foundation commissioned a panel comprised of 26 pediatric epileptologists and dietitians from nine countries with particular expertise using the KD. This group was created in order to create a consensus state-

ment regarding the clinical management of the KD. Subsequently endorsed by the Practice Committee of the Child Neurology Society, this resultant manuscript addresses issues such as patient selection, pre-KD counseling and evaluation, specific dietary therapy selection, implementation, supplementation, follow-up management, adverse event monitoring, and eventual KD discontinuation. This paper highlights recommendations based on best evidence, including areas of agreement and controversy, unanswered questions, and future research. **KEY WORDS:** Children, Consensus, Diet, Epilepsy, Ketogenic.

The ketogenic diet (KD) is a nonpharmacologic treatment used worldwide for children with intractable epilepsy

(Stafstrom & Rho, 2004; Kossoff & McGrogan, 2005; Freeman et al., 2007). It has been used to treat epilepsy in children since 1921 with little variation until recent years (Freeman et al., 2007). The original protocol using a high fat, low carbohydrate diet was created at the Mayo Clinic in Rochester, MN (Wilder, 1921), and popularized by the Johns Hopkins Hospital in Baltimore, MD (Freeman et al., 1998). The KD was traditionally started in the hospital after

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a 48-h fast followed by a gradual introduction of calories in the form of a KD over a 3-day period. Children were then seen periodically in clinic for medical and nutritional follow-up.

Over the past decade, however, there has been worldwide investigation into which children should be started on the KD, as well as the ideal protocol for its implementation and subsequent follow-up management. Unlike anticonvulsant therapy, there are many ways in which to provide the KD and each may be valid. With its inherent variability, there exists a need for standardized KD protocols both in order to guide neurologists and dietitians beginning to offer the KD in their individual centers as well as to guide multicenter research studies. At this time, there are no international KD recommendations, with published attempts made on a national level in Germany only to date (Klepper et al., 2004).

Recognizing that there is currently insufficient class I evidence for the majority of the clinical management issues regarding the KD to create a practice parameter (Henderson et al., 2006), The Charlie Foundation commissioned an international committee of neurologists and dietitians with expertise in the KD in December 2006 at the American Epilepsy Society meeting in San Diego, CA, U.S.A. The charge of this consensus group was to provide practical recommendations to guide management of the KD.

METHODS

Experts in the clinical use of the KD were identified by Jim Abrahams, founder of The Charlie Foundation, Beth Zupiec-Kania, RD, CD, Dietitian for The Charlie Foundation, and Eric Kossoff, MD, Medical Director of the Johns Hopkins Ketogenic Diet Center. Identified clinicians had at least one authored, peer-reviewed publication regarding the KD or were a member of a center that had published about the KD. Attempts were made to avoid more than three clinicians from any individual center. Twenty-six clinicians, of which seven (27%) were dietitians, were identified. Eleven (42%) participants were from outside the U.S.A. Dr. Kossoff and the other 24 experts (other than Ms. Zupiec-Kania) did not receive direct funds from The Charlie Foundation nor was this consensus statement subsidized in any way.

Participants were asked to write a section topic either individually or in pairs based on both their individual expertise and an outline of clinical issues created by the two primary authors (E.K. and B.Z.K.). Instructions were given to keep each section brief (2–3 paragraphs) and focus primarily on peer-reviewed publications when available. In the absence of published literature, the participants were asked to base recommendations on their professional or center's experience. Sections were collected (by E.K.), incorporated into a full document, and then emailed to the entire group for review.

As comments and changes were received by all consensus members regarding details of the recommendations, it became clear that there were certain topics that were more controversial than others. To convey these areas where consensus was not obtained, a short survey of 15 questions was then emailed to all 26 participants to obtain a group consensus. Results from this survey were then incorporated into the body of the manuscript, providing percentage responses for topics. Following this, all participants later reviewed the full manuscript again prior to submission. This consensus statement has been since endorsed by the Child Neurology Society who also reviewed the full manuscript.

CONSENSUS RECOMMENDATIONS

Patient selection

Most individuals who develop epilepsy will respond to pharmacologic treatment, however, approximately 20%–30% will develop medically refractory epilepsy (Sillanpää & Schmidt, 2006). For this population, “alternative” or nonpharmacologic treatments such as dietary therapy can be highly efficacious and should be seriously considered.

In the past, the use of the KD was limited by the scarcity of centers experienced in its use as well as lack of confidence in the diet's efficacy (Freeman et al., 2007). However, over the past decade the role of the KD in the treatment of intractable epilepsy has become evident from the increased number of publications available as well as the increased number of epilepsy centers that offer the KD (Kossoff & McGrogan, 2005; Henderson et al., 2006; Freeman et al., 2007).

The KD can effectively treat epilepsy in individuals from infancy through adulthood. For years it was thought that infants have difficulty maintaining ketosis while meeting their growth requirements, and they therefore were not routinely treated with the diet (Nordli et al., 2001). Adolescents and adults have typically not been considered candidates for KD treatment, although data for its benefit in these populations does exist (Barborka, 1930; Sirven et al., 1999; Mady et al., 2003; Kossoff et al., 2008a). When surveyed, 10 (38%) of the consensus group offered dietary therapy to adults. Regardless of age, seizure type, or etiology, the KD appears to provide a third of the patients with >90% reduction in their seizure frequency (Henderson et al., 2006).

Traditionally, the KD has been reserved as a “last treatment option” after establishment of medical intractability, typically defined as the failure of three or more anticonvulsant medications. Given its efficacy, the poor chance of improvement with further anticonvulsant trials, and the availability of more easily implemented alternatives such as the modified Atkins diet (Kossoff et al., 2006) and Low Glycemic Index Treatment (LGIT) (Pfeifer & Thiele, 2005), we propose that dietary therapy be considered earlier as an option for

Table 1. Epilepsy syndromes and conditions in which the KD has been reported as particularly beneficial

<p>Probable benefit (at least two publications)</p> <ul style="list-style-type: none"> Glucose transporter protein I (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 Children receiving only formula (infants or enterally fed patients) <p>Suggestion of benefit (one case report or series)</p> <ul style="list-style-type: none"> Selected mitochondrial disorders Glycogenosis type V Landau-Kleffner syndrome Lafora body disease Subacute sclerosing panencephalitis (SSPE)
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Table 2. Contraindications to the use of the KD

<p>Absolute</p> <ul style="list-style-type: none"> Carnitine deficiency (primary) Carnitine palmitoyltransferase (CPT) I or II deficiency Carnitine translocase deficiency β-oxidation defects <ul style="list-style-type: none"> Medium-chain acyl dehydrogenase deficiency (MCAD) Long-chain acyl dehydrogenase deficiency (LCAD) Short-chain acyl dehydrogenase deficiency (SCAD) Long-chain 3-hydroxyacyl-CoA deficiency Medium-chain 3-hydroxyacyl-CoA deficiency Pyruvate carboxylase deficiency Porphyria <p>Relative</p> <ul style="list-style-type: none"> Inability to maintain adequate nutrition Surgical focus identified by neuroimaging and video EEG monitoring Parent or caregiver noncompliance

treatment of difficult-to-manage epilepsy. When surveyed, 81% of the group believed that the KD should be offered to a child after two anticonvulsants are used unsuccessfully.

There are several specific conditions in which the group considered the KD could be used potentially even earlier (Table 1). The diet is the treatment of choice for two distinct disorders of brain energy metabolism: GLUT1 deficiency syndrome (Klepper & Leidencker, 2007) and pyruvate dehydrogenase deficiency (PDHD) (Wexler et al., 1997). In GLUT1 deficiency syndrome, glucose transport across the blood-brain barrier is impaired resulting in seizures, developmental delay, and a complex movement disorder (Klepper & Leidencker, 2007). Twenty-four members of the consensus (92%) believed the KD should be considered as a first-line therapy for GLUT1 deficiency syndrome. In PDHD, a severe mitochondrial disease with lactic acidosis and severe impairment, pyruvate cannot be metabolized into acetyl-CoA (Wexler et al., 1997). In both disorders, the KD provides ketones that bypass the metabolic defect and serve as an alternative fuel to the brain.

The KD has also been described as particularly useful for certain epilepsy and genetic syndromes as well. Myoclonic epilepsies, including severe myoclonic epilepsy of infancy (Dravet Syndrome) and myoclonic-astatic epilepsy, as described by Doose (Oguni et al., 2002; Laux et al., 2004; Caraballo et al., 2005, 2006; Kilaru & Bergqvist, 2007; Korff et al., 2007) appear to respond well to the KD. The KD can be beneficial in infants with West syndrome who are refractory to corticosteroids and other medications (Nordli et al., 2001; Kossoff et al., 2002b; Eun et al., 2006). There is evidence from three epilepsy centers for the benefits of the KD in tuberous sclerosis (Kossoff et al., 2005; Coppola et al., 2006a; Kossoff et al., 2007c; Martinez et al., 2007).

Preliminary experience also showing some beneficial effects of the KD have been reported in symptomatic epilepsies due to Lafora body disease (Cardinali et al., 2006), Rett syndrome (Haas et al., 1986; Liebhaver et al., 2003; Giampietro et al., 2006), Landau-Kleffner syndrome (Bergqvist et al., 1999), and subacute sclerosing panencephalitis (Bautista, 2003). Single reports describe the use of the diet in metabolic disorders such as phosphofructokinase deficiency (Swoboda et al., 1997), glycogenosis type V (Busch et al., 2005), and mitochondrial respiratory chain complex disorders (Kang et al., 2007a).

The KD is contraindicated in several specific disorders (Table 2). The metabolic adaptation to the KD involves a shift from use of carbohydrates to lipids as the primary energy source. As such, a patient with a disorder of fat metabolism might develop a severe deterioration in the setting of fasting or a KD. Therefore, before initiating the KD, a child must be screened for disorders of fatty acid transport and oxidation.

Long-chain fatty acids are transported across the mitochondrial membrane by carnitine, facilitated by carnitine palmitoyltransferase (CPT) I and II and carnitine translocase (Tein, 2002). Once in the mitochondrion, fatty acids are β -oxidized to two carbon units of acetyl-CoA that can then enter the tricarboxylic acid cycle and be utilized for energy production or ketone body formation. An inborn metabolic error at any point along this pathway can lead to a devastating catabolic crisis (i.e., coma, death) in a patient fasted or placed on a KD. Deficiency of pyruvate carboxylase, a mitochondrial enzyme that catalyzes the conversion of pyruvate to oxaloacetate, will impair tricarboxylic acid cycle function and energy production in patients on the KD. Finally, the KD is contraindicated in porphyria, a disorder of heme biosynthesis in which there is deficient porphobilinogen deaminase; the lack of carbohydrates in the KD can exacerbate acute intermittent porphyria. Contrary to prior anecdotal evidence, the KD has been reported in a

single case series as safe and efficacious in mitochondrial diseases, mostly those with Complex I disease (Kang et al., 2007a).

Clinical suspicion about an inborn error of metabolism includes developmental delay, cardiomyopathy, hypotonia, exercise intolerance, myoglobinuria, and easy fatigability (Sankar & Sotero de Menezes, 1999). The presence of one of those clinical features suggests that the child should be tested to rule out an inborn error of metabolism prior to KD initiation.

Although not a true contraindication, there is recent evidence that children with very focal epilepsy may do less well with the KD than resective surgery (Stainman et al., 2007). In this situation, the KD may offer a period of both reduced seizures and anticonvulsants, but only rarely a prolonged seizure-free response. The consensus group had mixed opinion on whether to offer the KD for a child with a clear surgically resectable lesion, with 15 (58%) providing the KD in this situation as long as the family was adequately counseled beforehand.

There are several uncontrolled trials and animal studies describing the potential benefits of the KD for neurologic conditions other than epilepsy and the metabolic conditions described previously. These include amyotrophic lateral sclerosis (ALS), Parkinson's disease, Alzheimer's disease, migraine, autism, narcolepsy, brain tumors, and traumatic brain injury (Freeman et al., 2007). At this time, there is insufficient evidence to recommend the use of the KD for these conditions other than on an investigational basis.

Committee conclusions

The KD should be strongly considered in a child who has failed two to three anticonvulsant therapies, regardless of age or gender, and particularly in those with symptomatic generalized epilepsies. It can be considered the treatment of choice for two distinct disorders of brain metabolism, GLUT-1 deficiency syndrome and PDHD. In the particular epilepsy syndromes of Dravet syndrome, infantile spasms, myoclonic-astatic epilepsy, tuberous sclerosis complex, the KD could be offered earlier. The KD is probably only of limited benefit in children who are candidates for epilepsy surgery. Before starting the KD, inborn errors of metabolism that could lead to a severe metabolic crisis should be ruled out. These include disorders of fatty acid mitochondrial transport, β -oxidation, and other mitochondrial cytopathies.

Prediet evaluation and counseling

A clinic visit prior to initiation of the KD is necessary and recommended. The goals of this visit are to identify the seizure type, rule out metabolic disorders that are contraindications to the diet, and evaluate for complicating factors (presence of kidney stones, dyslipidemia, liver disease, failure to thrive, gastroesophageal reflux, poor oral intake, constipation, cardiomyopathy, and chronic metabolic acidosis) (Table 3). The KD team should re-

view all current medications to determine carbohydrate content and options of switching to lower carbohydrate preparations.

Before starting the diet, it is crucial to also discuss psychosocial issues inherent in the KD. The physician should ensure that the parent or caregiver understands their involvement in administering the KD to their child, specifically the importance of strict adherence to the diet, avoidance of carbohydrates, need for multivitamin and mineral supplementation, and awareness of potential adverse effects. One should also identify any behavioral or personality traits in the child that will significantly challenge successful administration of the diet and determine any food allergies and intolerances and cultural/religious preferences that will need to be considered in meal plans.

Several laboratory studies are suggested before starting the KD (Table 3). If there is a personal or strong family history of kidney stones, a renal ultrasound and nephrology consultation should be obtained. As part of the diagnostic workup of a progressive epileptic encephalopathy, cerebrospinal fluid evaluation (for glucose, protein, lactate, folate metabolites, amino acids, and potentially neurotransmitters) as well as a full serum and urine metabolic evaluation should be performed if no clear etiology for the child's epilepsy has been identified. An electroencephalogram (EEG) and magnetic resonance imaging (MRI) will assist in identifying those patients who are possible surgical candidates; therefore, these investigations should be strongly considered.

A key component of the KD is the information the family receives prior to the initiation of the diet. Many families will have preconceived notions about what the KD is, how it will be initiated, and expectations of its efficacy, especially since families have different experiences while initiating the diet even within the same facility. Helpful resources for families include *The Ketogenic Diet: A Treatment for Epilepsy in Children and Others* (Freeman et al., 2006) and publications and videos from support groups such as The Charlie Foundation and Matthew's Friends. High glycemic carbohydrate foods can be reduced slightly in advance of the KD to prepare the child for the dietary change.

It is important for the ketogenic team to thoroughly discuss parental expectations in advance of KD initiation to ensure its success. Many families expect not only seizure reduction, but also medication reduction and cognitive improvement (Farasat et al., 2006). The team should keep the expectations realistic for each individual child. The expected length of time on the KD if successful is often a concern that the family wishes to discuss prior to starting the KD and a minimum of 3 months (to allow for potential improvement to occur) should be suggested. The family should know what challenges they may face both short- and long-term, such as possible nausea, vomiting,

Table 3. Recommendations for pre-KD evaluation

<p>Counseling</p> <ul style="list-style-type: none"> 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 read parent-oriented KD information <p>Nutritional evaluation</p> <ul style="list-style-type: none"> 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 (MCT, classic, modified Atkins, or low glycemic index) Calculation of calories, fluid, and ketogenic ratio (or percentage of MCT oil) Establish nutritional supplementation products based on dietary reference intake <p>Laboratory evaluation</p> <ul style="list-style-type: none"> 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 <p>Ancillary testing (optional)</p> <ul style="list-style-type: none"> Renal ultrasound and nephrology consultation (if a history of kidney stones) EEG MRI Cerebrospinal fluid (CSF) (if no clear etiology has been identified) EKG (echocardiogram) if history of heart disease

behavioral outbursts, and various other medical complications, and how to address these issues if they arise. A social worker on the team can be instrumental in helping the family transition to the KD by assessing family needs, gathering resources, and contacting other families on the KD for parent-to-parent support.

It is also important for the family to know what to expect during the hospital stay, such as whether tests (such as EEG) or medical interventions (such as intravenous fluids) are likely. Parents are allowed to bring games and books to help keep the child comfortable during this time. Topics including meal preparation, managing sick days, traveling, celebrations, and nutritional supplements can be discussed during the training.

Committee conclusions

There are several important prerequisites to starting the KD to ensure both safety and to maximize the chances of success (Table 3).

Specific diet selection and provision

There has often been discussion as to whether there is an optimal way to administer the KD. The classic (long chain triglyceride or LCT) diet has been the more traditional KD treatment, for which most data are available, but the medium chain triglyceride (MCT) diet may be preferable in some cases (Huttenlocher, 1976; Schwartz

et al., 1989; Neal et al., 2008). In the classic KD, fat is a LCT and obtained primarily from standard foods, protein is based on minimum requirements for growth, and carbohydrates are restricted. MCT oils yield more ketones per kilocalorie of energy than their long chain counterparts; they are absorbed more efficiently and carried directly to the liver. This increased ketogenic potential means less total fat is needed in the MCT diet, thus allowing inclusion of more carbohydrate and protein. Data from studies 20 years apart now suggest no difference in efficacy between the two diets if applied appropriately in a calculated fashion (Schwartz et al., 1989; Neal et al., in press). There may be some differences in tolerability but this did not reach statistical significance in a recent randomized controlled trial with direct comparison between the two (Neal et al., in press).

The classic KD is calculated in a ratio of grams of fat to grams of protein plus carbohydrate. The most common ratio is 4 g of fat to 1 g of protein plus carbohydrate (described as "4:1"). This means that 90% of the energy comes from fat and 10% from protein and carbohydrate combined. Sometimes it is necessary to provide the KD at a lower ratio to increase protein or carbohydrate intake. There is some evidence that a 4:1 ratio, when used at initiation, may be more advantageous for the first 3 months (Seo et al., 2007).

Calories are typically restricted to 80%–90% of the daily recommendations for age; however, this has never been shown in patients to be beneficial (Vaisleib et al., 2004). Additionally, an underweight child should be started at calories based on current weight then increased gradually over time. An overweight child should be allowed to grow to appropriate length for weight rather than incurring weight loss, although in some children attaining a more ideal body weight may be nutritionally indicated. Similarly, fluid restriction to 90% is also based on historical use of the diet rather than on scientific evidence. Many centers no longer fluid restrict children on the KD.

The traditional MCT diet comprises 60% energy from MCT. This level of MCT can cause gastrointestinal discomfort in some children, with reports of abdominal cramps, diarrhea, and vomiting. For this reason, a modified MCT diet was developed, using 30% energy from MCT, with an additional 30% energy from long chain fat. In practice, a starting MCT level somewhere between the two (40%–50% energy) is likely to be the best balance between gastrointestinal tolerance and good ketosis. This can be increased or decreased as necessary during fine-tuning; many children will tolerate 60% or higher energy from MCT and need this amount for optimum ketone levels and seizure control. MCT oil has also been used to augment the traditional KD to stimulate ketones and for its beneficial laxative property. MCT can be given in the diet as oil, as coconut oil, or as an emulsion (Liquigen, SHS, Liverpool, U.K.). MCT should be included in all meals when used. Less quantity of MCT with each meal, with more meals per day, may improve tolerance.

The KD may be delivered as an all-liquid, formula-based diet (Kossoff et al., 2004a; Hosain et al., 2005). Tolerability and adverse effects of the KD in infants is similar to that in older children. The KD may also be easily administered to enterally fed children. As expected, enterally (including gastrostomy and jejunostomy) fed children demonstrate very high compliance rates, exceeding those in most solid food KD series, and efficacy is also high (Kossoff et al., 2004a; Hosain et al., 2005). Prescription of a formula-based KD is generally simpler for dietitians to calculate, requires less education of families and caregivers, and due to the ease of delivery of an all-liquid KD, ketosis is easily maintained as errors are less common.

To prepare a formula-based KD, three commercial products are currently available. KetoCal (for North America: Nutricia, Rockville, MD, U.S.A. and for Europe: SHS) is a milk protein-based, powdered formula to which water is added. This provides either a 3:1 or 4:1 KD; however, fat and protein modulars may be added to customize the diet for each child. Ross Carbohydrate Free[®] Soy Formula Base With Iron (Abbott Nutrition, Columbus, OH, U.S.A.), which provides protein, some fat, and vitamins and minerals, may also be combined with a carbohydrate polymer such as Polycose powder (Abbott Nutrition), and a lipid

emulsion such as Microlipid[®] (Nestle, Vevey, Switzerland) to add the needed fat to achieve the goal KD ratio. In addition, water must be added to Ross Carbohydrate Free formula for proper dilution. Both combinations are fortified with vitamins and minerals; however each should be compared to age-appropriate requirements and supplemented to meet the Dietary Reference Intakes (DRI) established by the National Academy of Sciences. In addition, a formula may also be created from pureed infant foods with the addition of a liquid fat source, diluted with water, and supplemented with micronutrients. This formula may be necessary when allergies to both soy and milk protein formulas are present.

In the past few years, two other dietary therapies have been developed for the treatment of epilepsy: the modified Atkins diet and LGIT (Pfeifer & Thiele, 2005; Kossoff et al., 2006; Kang et al., 2007b; Kossoff et al., 2007b). Unlike the classic KD, both of these dietary therapies are initiated without an inpatient hospital stay and they do not require precise weighing of food ingredients and portions. Both diets require less dietitian time for meal calculations, but more parental independence. All but one member of the consensus group (96%) offers these diets to children.

The modified Atkins diet is similar to the classic KD in its composition and is approximately a 1:1 ketogenic ratio (Kossoff et al., 2006). The initial daily carbohydrate consumption on the modified Atkins diet is approximately 10 g (comparable to the strict initiation phase of the Atkins diet used for weight loss), with a planned increase to 15–20 g/day after 1–3 months (Kossoff et al., 2007b). However, there are no limitations on protein, fluids, and calories; making meal planning easier.

The LGIT was developed following the observation that children on the classic KD have stable blood glucose levels and the hypothesis that this may relate at least in part to the mechanism of the KD (Pfeifer & Thiele, 2005). The LGIT allows liberalization of total daily carbohydrate intake to approximately 40–60 g/day, but regulates the type of carbohydrate, favoring those that produce relatively small changes in blood glucose (those with low glycemic indices <50).

Small, uncontrolled reports suggest that both modified diets show efficacy rates similar to the classic KD. These diets may also be of value for adolescents and adults not typically offered the traditional KD. In fact, 11 (42%) of the consensus group believed these diets should be used primarily when treating adolescents. Larger, randomized studies are needed to better understand the efficacy and tolerability of these diets, how they compare to the classic KD, and potential use in adults.

Committee conclusions

There is no evidence of increased efficacy of MCT versus LCT, therefore which KD is chosen should be based on the dietary needs and habits of the individual child,

although it may be influenced by the experience of the team involved. An all-liquid, formula-based KD is recommended for use in infants who have not yet transitioned to solid foods and for individuals fed enterally. There is preliminary evidence for the use of both the less restrictive modified Atkins diet and LGITs, but the optimal patient populations for these diets have not yet been identified. These latter two therapies may be advantageous for adolescents and adults.

Diet initiation

The KD initiation practices have their origin in the historical use of periodic fasting to treat seizures. Fasting is therefore part of the KD initiation in many centers worldwide. Because of concerns that fasting may result in hypoglycemia, acidosis, nausea, vomiting, dehydration, anorexia, lethargy, and a small risk for increase in seizures, most centers begin the KD in the hospital so that the patient can be closely observed, and medical interventions can be instituted if necessary. Hospitalization also provides the opportunity for intensive teaching of the caregivers on how to calculate, weigh, design meals, and manage the KD at home.

The traditional method of initiating the KD involves a period of fasting, with no carbohydrate-containing fluids provided, and serum glucose monitored periodically (Freeman et al., 2006). The duration of fasting varies from 12 h to “when urine ketones are large,” which can be longer than 48 h. Children should not be fasted longer than 72 h. The meals are then typically advanced daily in one-third caloric intervals until full calorie meals are tolerated, while keeping the KD ratio constant. Another approach begins with full calories, but the KD ratio increases daily from 1:1, 2:1, 3:1, to 4:1 to allow the patient to acclimate to the increasing concentration of fat (Bergqvist et al., 2005).

In most clinical trials of KD efficacy, a fasting initiation protocol was used. However, there is now retrospective (Kim et al., 2004) and prospective data indicating that fasting is not necessary for achievement of ketosis, and that gradual initiation protocols offer the same seizure control at 3 months with significant lower frequency and severity of initiation related side effects (Bergqvist et al., 2005). In addition, weight loss, hypoglycemia, and acidosis were less common when children were not fasted in this study (Bergqvist et al., 2005). Vomiting did not differ in the two protocols, but intravenous fluids for dehydration were more commonly needed in the fasting group. Continued use of fasting protocols is therefore based on the centers' individual practice rather than a need for seizure control. Some older as well as recent evidence suggests that fasting does lead to a quicker onset of seizure reduction, and therefore may be advantageous when a more immediate response is desired (Freeman & Vining, 1999; Kossoff et al., 2008b). There was a difference of opinion between members of the consensus group in regards to fasting. Fifteen

(58%) members believed fasting was not necessary but did have benefit, eight (31%) did not believe fasting should be used, and three (11%) stated that fasting should be universally used when starting the KD.

The main reasons for inpatient initiation include safety (management of acute medical side effects) and education of care providers. Twenty-three members (88%) routinely admit children for initiation of the KD. However, it is possible to start the KD as an outpatient, based on two retrospective studies encompassing 8 and 37 patients, respectively, in which no fasting period was used (Wirrell et al., 2002; Vaisleib et al., 2004). Although there were no serious side effects related to unmasking an underlying metabolic disorder with an outpatient approach, the size of these samples is too small to expect discovery of relatively rare disorders.

The potential advantages of an outpatient, gradual KD initiation include less stress for the child, no absence from the home for the care providers, and significantly reduced costs associated with hospitalization. However, to provide the KD initiation as an outpatient, all children must be screened completely prior to starting the KD with metabolic testing, the child must be in close proximity to medical care, and the KD team must be able to provide all the family education in an outpatient setting. Although as stated previously, most centers still routinely admit for KD initiation, 19 (73%) members believed that an outpatient initiation could be used in very select situations.

Committee conclusions

At this time, there is evidence that the traditional KD protocol can be altered successfully to ease its implementation. Fasting may be appropriate when a quicker time to response is desired, but is not necessary for long-term efficacy, and may have more immediate side effects. In select situations, the KD can also be started as an outpatient.

Medications and the KD

The KD is traditionally used in patients who have failed to respond to anticonvulsant medications. Specifically, it is customary to add the KD to an existing regimen of drugs. Hence, with the exception of patients whose drugs are eventually discontinued due to an excellent response to the KD, little is known about both the efficacy and tolerability of the KD without the confound of concomitant medications. Surprisingly, despite decades of combined use of anticonvulsants and the KD, it remains unclear whether there are negative or positive pharmacodynamic interactions, and only scant information regarding the impact of the KD on the pharmacokinetics of anticonvulsants.

At present, there are no data supporting any significant pharmacodynamic interactions between anticonvulsant drugs and the KD. That is, no particular combination of anticonvulsants and the KD have been shown to yield either greater or less efficacy in terms of seizure protection at this time. The KD may have synergistic benefits

when used in combination with a nonpharmacologic therapy; namely vagus nerve stimulation (VNS) (Kossoff et al., 2007a). Serum levels of commonly used anticonvulsant agents, when corrected for changes in dose and weight (i.e., plasma concentration in relation to the dose per kilogram of body weight per day), do not appear to be altered by the KD (Dahlin et al., 2006).

There is a historical perception that valproic acid should not be used together with the KD. This stems from the concerns for idiosyncratic side effects of valproic acid (i.e., hepatotoxicity) and for the fact that this medication is a short-chain fatty acid. Clinicians have generally feared that enhanced fatty acid oxidation, a consequence of using the high-fat KD, might increase the risk of hepatotoxicity. Despite such fears, recent clinical evidence supports the safe use of valproic acid and the KD (Lyczkowski et al., 2005). But while idiosyncratic adverse reactions are not necessarily heightened, it does appear that secondary carnitine deficiency, which can occur with either the KD or valproic acid alone, can be worsened (Coppola et al., 2006b).

The KD is also known to cause a transient but often clinically asymptomatic metabolic acidosis. Adding the KD to an existing regimen of carbonic anhydrase inhibitors (topiramate and zonisamide) may in fact worsen preexisting metabolic acidosis, but the greatest decreases in serum bicarbonate levels occur early after initiation of the diet (Takeoka et al., 2002). It is recommended that bicarbonate levels should be monitored carefully, especially when receiving these anticonvulsants, and that bicarbonate supplements be given when patients are clinically symptomatic (vomiting, lethargy). There may be health benefits, specifically to bone density, in the use of bicarbonate supplements for children with acidosis, but this has not been proven. It does not appear that carbonic anhydrase inhibitors, which can increase the risk of kidney stones separately, have an increased likelihood of stones when used in combination with the KD (Kossoff et al., 2002a). However, it is wise to observe children for stones more carefully when on carbonic anhydrase inhibitors and perhaps empirically start oral citrates such as Polycitra K (Cypress Pharmaceuticals, Madison, MS, U.S.A.) (Sampath et al., 2007). There is no evidence for routine renal ultrasound surveillance, however, or automatic discontinuation of these anticonvulsants prior to KD initiation.

Discontinuing medications is often a major goal of the KD and typically advised after several months of success. However, there is evidence that anticonvulsants can be reduced successfully even during the first month of the KD (Kossoff et al., 2004b). Seizure exacerbations are more likely when phenobarbital or benzodiazepines are the anticonvulsants weaned, so caution is recommended when these medications are tapered.

Finally, ingestion of carbohydrates can quickly reverse the ketosis achieved by the KD in some children and may lead to resumption in seizure activity (Huttenlocher,

1976). Clinicians should be mindful that formulations of many drugs, including nonanticonvulsants, contain carbohydrates or sugars as additives (Lebel et al., 2001), and should seek alternatives whenever possible.

Committee conclusions

At this time, there is little evidence of any consistent positive interactions between the KD and anticonvulsants. The KD may work well in combination with VNS. Conversely, the KD is not negatively affected in regards to efficacy or side effects by any particular anticonvulsant. Medications can often be reduced within the first few months if the KD is successful, although caution is advised especially when reducing phenobarbital and benzodiazepines.

Diet supplementation

Sufficient vitamins and minerals are normally found in a well-balanced diet, however due to the limited quantities of fruits, vegetables, enriched grains, and foods containing calcium on the KD, supplementation is essential, especially for B vitamins (Table 4). There is little vitamin D and calcium in KD food and evidence for decreased Vitamin D levels in children with epilepsy, and therefore both vitamin D and calcium should be supplemented (Bergqvist et al., 2007). Additional supplementation (e.g., zinc, selenium, magnesium, phosphorus) was suggested by some group members, but at this time there is insufficient evidence to recommend their use above what is provided in a standard multivitamin.

Carbohydrate-free or minimal carbohydrate-containing multivitamin and mineral products should be used. Some vitamins and supplements that will be discussed may have limited availability based on individual country. In the U.S., commonly used preparations include Centrum (Wyeth, Madison, NJ, U.S.A.) and Bugs Bunny Sugar-free (Bayer, Morristown, NJ, U.S.A.). Multibionta (Seven Seas, Marfleet, U.K.) is a multivitamin supplement also available as a liquid formulation. A relatively new vitamin designed for the KD and allergy population is called NanoVM (Solace Nutrition, Rockville, MD, U.S.A.). This product

Table 4. Supplementation recommended for children receiving the KD

Universal recommendations
Multivitamin with minerals (and trace minerals)
Calcium with vitamin D
Optional extra supplementation
Oral citrates (Polycitra K)
Laxatives: Miralax, mineral oil, glycerin suppository
Additional selenium, magnesium, zinc, phosphorus, vitamin D
Carnitine (Carnitor)
MCT oil or coconut oil (source of MCT)
Salt (sodium to add to modular formulas if used for greater than age 1 year)

All supplements listed should be provided as carbohydrate-free preparations whenever possible.

is virtually carbohydrate-free, is formulated to meet 100% of the micronutrient needs of children, and is available in two preparations for ages 1–3 and 4–8 years.

There is evidence for the preventative use of oral citrates (Polycitra K more so than Bicitra) in regards to reducing the risk of kidney stones. In a retrospective study, the risk was reduced three-fold with their use; many children who presented with renal stones in this study had not been started on Polycitra K, despite occasionally borderline elevations in their urine calcium to creatinine ratio (Sampath et al., 2007). The empiric use of citrates in all children on the KD may be sensible, but has not been tested prospectively in a controlled manner for kidney stone prevention. Citrates may also reduce acidosis and theoretically bone mineral loss; however, there is evidence that folic acid absorption is reduced in an alkaline environment induced by bicarbonate use, which may increase the risk for megaloblastic anemia (Benn et al., 1971).

Gastrointestinal dysmotility can be a common side effect of the KD; however, empiric supplementation to alleviate this has not been studied. Children are often started on H2-blockers or proton pump inhibitors for gastroesophageal reflux, but most commonly after this condition occurs. Constipation is even more common on the KD, and parents should be aware of prevention techniques including the use of higher fiber vegetables, sufficient fluids, and if necessary, the use of carbohydrate-free laxatives.

Carnitine supplementation has been a controversial issue, with variability in its use between many centers worldwide. Secondary hypocarnitinemia can cause serious systemic complications such as hepatitis and cardiomyopathy, although the incidence is quite low (Berry-Kravis et al., 2001). Relatively common symptoms indicating hypocarnitinemia are generalized weakness, excessive fatigue, and decreased muscle strength, which are common in many patients with intractable epilepsy. Prolonged use of anticonvulsants such as valproic acid, poor nutritional status, and long-term use of KD are the causes of secondary hypocarnitinemia, especially in younger patients (Coppola et al., 2006b). Laboratory measurement of serum carnitine is not easily feasible in some countries. Carnitine supplementation may also be expensive if not covered by insurance and adds an additional medication that is often dosed three times a day. Seventy-seven percent of the consensus group obtains baseline carnitine levels, and 81% check levels at follow-up visits. The majority recommends that carnitine should only be supplemented orally if either levels are low (65%) or children become symptomatic (27%).

Committee conclusions

There is evidence for the use of low-carbohydrate multi-vitamin and mineral supplements in the routine use of the KD. There is no evidence for the empiric use of antacids, laxatives, or carnitine with the KD. Oral citrates appear to

be preventative for kidney stones, but its empiric use has not yet been established as beneficial.

Maintenance of children receiving the KD

The child on the KD should be seen regularly for follow-up evaluation by both dietitian and neurologist familiar with the KD (Table 5). At discharge, the parents should be given specific contact phone numbers and e-mail addresses for the KD team, especially the dietitian. The child should be seen initially at least every 3 months after hospital discharge with follow-up contact in the interim, especially if expected urinary ketosis is not maintained. A child under 1 year of age may be seen back in 2–4 weeks and should have more frequent contact with the KD team. Other children that may require extra attention include those with cerebral palsy, whose growth parameters are at or less than the fifth percentile, and any child with continued difficulty consuming the KD or with an illness shortly after KD initiation. After 1 year on the KD, visits can be spaced out to every 6 months with phone contact in the interim.

At this time, the majority (96%) of the consensus group advocates routine urine ketosis evaluation by parents several times per week. There is limited data regarding the value of serum β -hydroxybutyrate (BOH), with one study suggesting that serum BOH may better correlate with seizure control (Gilbert et al., 2000). Many members of the consensus group believed that obtaining serum BOH at routine KD clinic visits was valuable, but only four (15%) suggested parents use home BOH meters. It is reasonable to obtain serum BOH in clinical situations where urine ketosis does not correlate with expected seizure control (e.g., absent urinary ketosis despite seizure freedom or large urinary ketosis in the setting of worsening seizures).

In addition to a complete examination, including accurate growth parameters such as weight and height, laboratory studies are recommended. Special attention is given to serum albumin and total protein concentration to ensure the KD is providing enough protein and calories. Fasting cholesterol and triglyceride levels typically rise and should be monitored. Decisions regarding withdrawal of anticonvulsants depends on the child's response to the diet (see previous section). The majority of centers do not obtain routine renal or carotid ultrasounds, echocardiograms, or bone mineral density evaluations. Nine (35%) consensus members routinely check an EEG after several months on the KD.

While receiving the KD, there needs to be ongoing nutritional support and management. Caloric intake and growth parameters should be reviewed at least every 3 months for the first year on the KD to ensure appropriate weight gain for age and length. Infants under 1 year of age should be monitored more frequently to prevent growth disturbance (Vining et al., 2002). If a child is overly hungry or not eating their meals, calories should be adjusted accordingly. There is no evidence that excessive weight gain or loss

Table 5. Recommendations for aspects of a follow-up KD clinic visit^a

Nutritional assessment (registered dietitian)
Obtain height weight, ideal weight for stature, growth velocity, BMI when appropriate
Review appropriateness of diet prescription (calories, protein, and fluid)
Review vitamin and mineral supplementation based on dietary reference intake guidelines
Assess compliance to therapy
Adjust therapy if necessary to improve compliance and optimize seizure control
Medical evaluation (neurologist)
Efficacy of the diet (is the KD meeting parental expectations?)
Anticonvulsant reduction (if applicable)
Should the KD be continued?
Laboratory assessment
Complete blood count with platelets
Electrolytes to include serum bicarbonate, total protein, calcium, magnesium, and phosphate
Serum liver and kidney profile (including albumin, AST, ALT, blood urea nitrogen, creatinine)
Fasting lipid profile
Serum acylcarnitine profile
Urinalysis
Urine calcium and creatinine
Anticonvulsant drug levels (if applicable)
Optional
Serum β -hydroxybutyrate (BOH) level
Zinc and selenium levels
Renal ultrasound
Bone mineral density (DEXA scan)
EEG

^aVisits should be at least every 3 months for the first year of the KD.

adversely affects KD effectiveness for seizure control, however (Hamdy et al., 2007).

The ketogenic ratio for the classic KD and percentage MCT oil for the MCT diet may also be adjusted upwards in the case of decreased ketosis and loss of seizure control, and lowered in situations of diet intolerability, severe dyslipidemia, poor linear growth, or excessive ketosis resulting in lethargy. A single study evaluating a planned decrease from a 4:1 to 3:1 ratio after 3 months found no loss of seizure control by this change or significant improvement in seizure control by increasing the ratio (Seo et al., 2007). Ratios higher than 4.5:1 are generally not used for more than a few months, because of the increased risk of adverse effects and poor compliance. Lowering the ratio to 2:1 or 1:1 can be implemented for children who are experiencing extreme difficulties adhering to the stricter ratios, particularly older adolescents and teenagers. Liberalizing the diet in this manner is similar to implementing the low glycemic index or modified Atkins approaches (Pfeifer & Thiele, 2005; Kossoff et al., 2006).

Liberalization of fluid should be considered for patients at increased risk for dehydration, such as those with increased activity, febrile illness, or exposure to warm temperatures, as well as infants. Low carbohydrate diets have a diuretic effect and in addition, unlike a normal diet, the contribution of fluid from the restricted volume of foods in the KD is minimal. It is helpful for families to be counseled

on appropriate fluid volume as a daily goal. If appropriate fluid intake cannot be met, a urine specific gravity within normal limits (<1.015) is a good measure of adequate hydration.

At each clinic visit, but definitely according to the consensus group after a median of 2 years (range: 0.5–4 years), a thorough reevaluation of the KD risks and benefits should be considered. Parents should be allowed a primary decision-making role in deciding how long to maintain the KD for their child unless there are clear medical concerns.

Committee conclusions

Ongoing clinic visits at least every 3 months for the first year with ready access to experienced advice are important for successful management of children receiving the KD. More frequent visits may be necessary for infants and other patients at high risk for nutritional deficiency. All children should be seen by an experienced pediatric neurologist and dietitian and have a nutritional assessment, laboratory evaluation, and discussion regarding KD and anticonvulsant discontinuation decisions.

Adverse effects of the KD

Although there have been numerous clinical trials of the KD, adverse events have not been consistently reported in these studies. However, side effects of the diet do occur, and neurologists and dietitians need to be observant (Ballaban-Gil et al., 1998; Wheless, 2001).

Metabolic abnormalities are relatively minor side effects of the KD and include hyperuricemia (2%–26%), hypocalcemia (2%), hypomagnesemia (5%), decreased amino acid levels and acidosis (2%–5%) (Schwartz et al., 1989; Chesney et al., 1999; Kang et al., 2004). Gastrointestinal symptoms including vomiting, constipation, diarrhea, and abdominal pain occur in 12%–50% of children (Kang et al., 2004). Carnitine deficiency has also been demonstrated, as described previously (Berry-Kravis et al., 2001). Hypercholesterolemia has been reported in 14%–59% of children on the KD (Chesney et al., 1999; Kwiterovich et al., 2003; Kang et al., 2004).

Renal calculi occur in 3%–7% of children on the KD (Furth et al., 2000; Kossoff et al., 2002a; Sampath et al., 2007). Stone composition includes uric acid (50% of stones), calcium oxalate, calcium phosphate, and mixed calcium/uric acid stones. They typically do not require diet discontinuation and lithotripsy is only rarely necessary. As previously stated, Polycitra K appears to help prevent stone formation (Sampath et al., 2007).

There is conflicting data on the effect of the KD on growth in children. One retrospective review of linear growth found that 86% of children on the diet had slowed growth, and this effect was independent of mean age, length of time on the diet, or protein and energy intake per body weight (Williams et al., 2002). A prospective study of 237 children found that the while older children grew “almost normally”; younger children grew poorly (Vining et al., 2002). There does not appear to be a difference between diets used despite the greater protein content of the MCT diet (Neal et al., in press).

Cardiac abnormalities have been reported, most anecdotally, in children on the KD, including cardiomyopathy and prolonged QT interval (Best et al., 2000; Bergqvist et al., 2003; Kang et al., 2004). The mechanism of these complications is unknown; one case was associated with selenium deficiency, but others were not. Pancreatitis has also been reported (Stewart et al., 2001; Kang et al., 2004).

The long-term complications in children maintained on the KD for greater than 2 years have not been systematically reviewed; there is only one report in the literature looking at this small subgroup (Groesbeck et al., 2006). In this population, there was a higher risk of bone fractures, kidney stones, and decreased growth, but dyslipidemia was not identified (Groesbeck et al., 2006). It may be advantageous in any child receiving the KD for long-term use, or anticonvulsants for that matter, to have periodic dual energy x-ray absorptiometry (DEXA) screening for bone health. In particular, the long-term effects of this high-fat diet on the cardiovascular system remain to be determined.

There were no particular adverse effects that the consensus felt strongly should lead to automatic diet discontinuation. All members believed that the adverse effects of the KD need to be considered always in comparison to its benefits for each individual child.

Consensus conclusions

Like all medical therapies, the KD has potential adverse effects. Overall, the risk of serious adverse events is low, and the KD does not need to be discontinued for these reasons for most children. However, physicians need to be aware of these potential risks so they can properly counsel parents and monitor children for the development of these complications.

KD discontinuation

The timing and actual method of KD discontinuation are often individualized based on patient response to the diet. Most parents are counseled to continue the KD, even if apparently ineffective, for at least 3 months (Freeman et al., 2006). The consensus group agreed that the KD should be used for at least a mean of 3.5 months (SD 2.2 months) before considering discontinuation. Recent data suggests that the KD works rapidly when effective, with 75% of children responding within 14 days (Kossoff et al., 2008b), so shorter KD durations may be adequate to assess efficacy. Should seizures worsen for more than a few days after starting the KD, similar to anticonvulsants, it could be discontinued immediately. If a family chooses to remain on the KD for longer than 6 months despite no apparent seizure control, the decision is ultimately their own and should be supported.

In children with >50% seizure response, the KD is often discontinued after approximately 2 years; however, in children in whom seizure control is nearly complete (e.g., >90% seizure reduction) and side effects are low, the diet has been reported as helpful for as long as 6–12 years (Groesbeck et al., 2006). This 2-year period is traditionally based on a similar time period used for anticonvulsant drugs, which are often discontinued after that time in children who become seizure-free. Children with GLUT-1, PDHD, or tuberous sclerosis complex may require longer KD durations than other conditions. Nineteen (73%) members routinely obtain an EEG prior to a planned KD discontinuation. For those in whom the diet has led to seizure freedom, 80% of children will remain seizure-free after the diet has been discontinued (Martinez et al., 2007). However, the risk of recurrence is higher in those with epileptiform EEGs, structural abnormalities on neuroimaging, and tuberous sclerosis complex (Martinez et al., 2007).

Although the diet can be discontinued abruptly in an emergency, typically in an intensive care unit, it is more often tapered slowly over 2–3 months by gradually lowering the ketogenic ratio from 4:1 to 3:1 to 2:1, then ketogenic foods are continued, but calories and fluids are increased ad libitum. Once urinary ketosis is lost, high carbohydrate foods can be reintroduced. This recommendation is based on traditional practice patterns, and mimics the several week gradual wean of anticonvulsant drugs (Freeman et al., 2006). During this time period, the group recommends continued nutritional supplementation. If seizures

worsen, the KD can be increased to the previously effective formulation. In the majority (58%) of these cases, seizure control can once again be attained with either KD or anti-convulsants (Martinez et al., 2007).

Committee conclusions

Consideration should be given to discontinue the KD after 3 months if unsuccessful, and 2 years if completely successful, but longer diet durations are necessary for GLUT-1 and PDHD and may be perfectly appropriate based on individual responses for intractable epilepsy. Prior to diet discontinuation in seizure-free children, a routine EEG and review of clinical data should be performed to counsel families regarding recurrence risk, which is 20% overall. Children with an epileptiform EEG, abnormal MRI, and tuberous sclerosis complex are at higher risk. During discontinuation, the group generally recommends a gradual wean over 2–3 months as outlined above, unless an urgent discontinuation of the diet is indicated.

CONCLUSIONS

This consensus statement represents the first international effort to identify commonalities in the clinical use of the KD. The majority of this group agreed on most of the major issues in both choosing the best candidates for the KD, counseling families before starting, supplementation, and the management of children on the KD in regards to nutrition, laboratory values, potential side effects, and eventual discontinuation. Areas of variability included primarily which diet to start (classic, MCT, modified Atkins, or LGIT) and how to initiate the KD (inpatient versus outpatient, fasting versus gradual). The creation of this consensus suggests that multicenter and multinational KD research protocols could be designed for specific epilepsy syndromes, with uniform consent and KD management between research sites. Additionally, these results indicate that there are still significant areas of debate for future KD research, specifically in regards to identifying the optimal methods of initiating the KD and use of alternative dietary therapies.

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APPENDIX 1. PRACTICE COMMITTEE OF THE CHILD NEUROLOGY SOCIETY

Anne Anderson, Bruce Cohen, Mary Currey, Diane Donley, Leon Dure, Bhuwan Garg, Michael Goldstein, Brian Grabert, David Griesemer, Edward Kovnar, Roger Larson, Agustin Legido, Leslie Anne Morrison, Colette Parker, J. Ben Renfroe, Juergen Schreck, Shlomo Shinnar, Russell Snyder, Carmela Tardo, G. Dean Timmons, and Gregory Yim.