STATE-OF-THE-ART REVIEW ARTICLE

The Ketogenic Diet: One Decade Later

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The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

The ketogenic diet, a high fat, adequate protein, low carbohydrate diet, has, during the past decade, had a resurgence of interest for the treatment of difficult-to-control seizures in children. This review traces its history, reviews its uses and side effects, and discusses possible alternatives and the diet's possible mechanisms of action. Finally, this review looks toward possible future uses of the ketogenic diet for conditions other than epilepsy.

www.pediatrics.org/cgi/doi/10.1542/peds.2006-2447

doi:10.1542/peds.2006-2447

Key Words
ketogenic diet, pediatric epilepsy, mechanisms of action

Abbreviations
KD— ketogenic diet
MCT—medium-chain triglyceride
LCT—long-chain triglyceride

Accepted for publication Oct 18, 2006

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THE KETOGENIC DIET (KD), developed in the early 1920s, had fallen into disuse during the 1970s and 1980s with the rapid development of new anticonvulsant agents for epilepsy.[1] The recent resurgence of interest and use of the diet can be dated to the American Epilepsy Society's meeting in 1996. Currently, it is perhaps more effective than most of the newer medications.

The rediscovery of this effective therapy for childhood epilepsy has, within the past decade, had a major impact on the most difficult-to-control seizures of childhood and promises to have an impact on adults with epilepsy as well. It will, perhaps, be used for other medical conditions as well. New research into its mechanism of action shows promise in changing our thinking about cerebral metabolism and our understanding of the control of epilepsy. This review was intended to document and summarize the remarkable progress in the use and understanding of the diet over the past 10 years. However, it is important to first understand its past.

HISTORY OF THE KD

1920–1990

In the early 1920s, epilepsy was treated with the bromides and phenobarbital. Both drugs had major sedating adverse effects and were frequently ineffective in completely controlling seizures. Hugh Conklin, an osteopathic physician and faith healer in Battle Creek, Michigan, believed, without any evidence, that epilepsy was attributable to intoxication of the brain from substances coming from the intestine.[2] He postulated that putting the intestine completely at rest would rid the body of the intoxication, and he thereby developed his "fasting" or "water treatment" for epilepsy. This treatment deprived the children with epilepsy of all food, giving nothing but water for as long as 25 days. In 1922, he reported a high percentage of cures, and many more children were free of seizures for prolonged periods of time.[2] But even before Conklin's report, word of his successful treatment had spread to others in more mainstream medicine.[3,4]

These reports promised hope for children with epilepsy and set off a flurry of clinical and research activity. Studies of the metabolic changes during fasting were undertaken in an attempt to understand the interrelationships of fat, protein, and carbohydrate metabolism. A review article at that time stated that ketone bodies caused by starvation were the immediate result of the oxidation of certain acids in the absence of sufficient glucose and postulated that they were anticonvulsant.[5]

Although prolonged fasting was difficult for those with severe epilepsy, it was far better than the constant seizures. The first article to suggest that a diet high in fat and low in carbohydrates could simulate the metabolic effects of starvation was published in 1921 from the Mayo Clinic.[4] This diet provided adequate protein for growth, minimal carbohydrate, and the remainder of the calories as fat and was virtually identical to the KD that is used today.

Reports of the effectiveness of this new "ketogenic" diet appeared throughout the next 2 decades until phenytoin (Dilantin) was discovered in 1938, and the attention of physicians and epilepsy researchers turned from the mechanisms of action and efficacy of the diet to the development and mechanisms of action of new anticonvulsant agents.[6] The era of medication treatment for epilepsy had begun, and the KD, then thought to be relatively difficult, rigid, and expensive, fell by the wayside. Encouraged by the drug companies, physicians believed that new and more effective medications were on the horizon. As pediatric neurologists and epileptologists had less and less experience with the "classical" KD, fewer children were started on it, and fewer dieticians were trained in its rigors and nuances. Therefore, the diets prescribed were often less precise, rigorous, and effective than in previous years. These failures led to the widespread opinion that the diet did not work and was very difficult to tolerate. A review of the KD in 1995 cited the feelings of many physicians that the KD was no longer justified.[7]

The Early 1990s

The KD had continued to be implemented in ~10 children each year at Johns Hopkins Hospital, initially under the direction of Dr Samuel Livingston and, subsequently, Dr John Freeman and their dietician Millicent Kelley.[8] In the late 1980s, in response to a challenge from a recently graduated nutritionist who asked if the diet was still effective in this "era of anticonvulsant medications," Kinsman[9] reviewed 58 recent patients and found that despite the use of many new anticonvulsant medications, patients with refractory seizures had the same success rate with the KD as had been reported decades earlier.

The start of the new era of the KD began with a Hollywood producer, Jim Abrahams, and his son Charlie, who was incapacitated by uncontrollable seizures that were refractory to multiple medications and other treatments. Reading about the diet, Abrahams brought his son to Johns Hopkins Hospital, and the child's seizures were stopped completely soon after starting the diet. To make other parents aware of the KD, Abrahams created the Charlie Foundation, which published a book about the KD, now in its fourth edition,[10] and made a film about the diet for parents and physicians.[11] NBC filmed a network television program (Dateline) about the diet in 1994, and Abrahams created a made-for-television movie, "First Do No Harm," starring Meryl Streep. In anticipation of these events, the Charlie Foundation funded a 7-center study of the diet designed to allow these centers to treat the patients resulting from the anticipated publicity.[12] The multicenter study was started in 1994 and presented to the American Epilepsy

Society in 1996. The reports from the multicenter study[12] and of 150 patients from Johns Hopkins[13,14] were the first of an avalanche of abstracts and articles on the clinical outcomes of children who were treated with the diet, including outcomes of various aspects and modifications of the diet. The amazing increase in the number of clinical abstracts presented at the American Epilepsy Society meetings is shown in Fig 1. Considering the time involved for new anticonvulsant medications to be developed, investigated, marketed, and then widely accepted, it is difficult to imagine now that just 10 years ago was the first time in recent years that an abstract on the KD was presented at the American Epilepsy Society.

1996–2006: The Explosion of Interest and Studies

Efficacy Demonstrated

Authors from Johns Hopkins reported the outcomes of 150 consecutive children 3, 6, and 12 months after initiating the diet,[13] as well as their 3- to 6-year follow-up[14] (Table 1). With an intention-to-treat methodology, these 150 children (who had averaged 410 seizures per month and whose seizures had failed to adequately improve on a mean of 6.2 medications) had a dramatic outcome. Twelve months after initiating the diet, 7% of the children were seizure free, and another 20% had a 90% decrease in seizures. Three to 6 years later, 27% of these same children had few or no seizures. Most of them were now off the diet and on fewer or even no medications.

Since the 1920s, reports of efficacy have been remarkably consistent across all age groups, seizure frequencies, and international locations.[15–18] In general, 10%–15% of children who initiated the diet were seizure free 1 year later, 30% had a >90% reduction in seizures, and 40% to 50% found that the diet was either too difficult to continue or insufficiently effective and therefore discontinued it during the first 6 months.

Although over the past decade there has been a dramatic increase in the number of anticonvulsant drugs available, the KD continues to demonstrate a higher degree of effectiveness, even in children whose seizures are refractory to these newer medications. Several recent meta-analyses have examined the publications about the diet and, although finding a lack of prospective controlled studies, found an enormous amount of prospective uncontrolled and retrospective evidence.[15–18] Nearly all reviews have stated that despite the lack of class I and II data, the scientific basis for the diet is strong and future studies should help identify ideal candidates and ways to improve tolerability rather than solely to prove the diet's efficacy in a controlled manner.[18]

Rise in Usage Internationally

Ten years ago the KD was nearly unknown internationally. In the past 8 years there has been a dramatic increase in its use worldwide, and currently ~75 centers in 45 countries offer the KD.[19] With the exception of parts of Central America and Africa, parents only need look to their country or a neighbor for a KD center. There have been sponsored conferences and symposia in Canada, Croatia, Cuba, England, Germany, Greece, India, and Italy in the past 2 years alone.

Cultural, religious, and financial differences among these centers have led to differences in approaches to providing the KD. Some use less or no fasting, some use different ratios (to encompass more rice and less fat in some countries in the East), and some allow increased fluid and calorie consumption.[19] These practices have led to insights into other methods for providing the KD that will be discussed later in this review. It should be noted that especially in developing nations, the KD may be a cost-effective epilepsy therapy when compared with the rising costs of anticonvulsant medications.

Challenges and Changes to the Traditional Diet Protocol

The Johns Hopkins protocol[10] for initiating and maintaining the KD has been gradually modified both at Johns Hopkins and other centers and is continually evolving. Highlights of its evolution and changes are shown in Table 2.

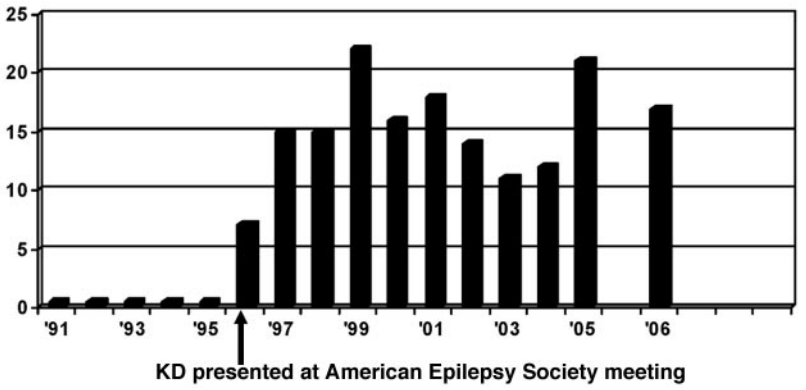

FIGURE 1
Number of abstracts regarding the KD presented at the American Epilepsy Society annual meeting each year, 1991–2006.

TABLE 1 **Outcomes of a 150-Patient Cohort Using the KD at Johns Hopkins Hospital**

	3 mo	6 mo	12 mo	3–6 y and Longer
Seizure reduction, *n* (%)				
Seizure free	4 (3)	5 (3)	11 (7)	20 (13)
90%–99%	46 (31)	43 (29)	20 (20)	21 (14)
50%–89%	39 (26)	29 (19)	34 (23)	24 (16)
<50%	36 (24)	29 (19)	8 (5)	18 (12)
No. (%) remaining on the KD	125 (83)	106 (71)	83 (55)	18 (12)

Sources: Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. *Pediatrics*. 1998;102:1358–1363; and Hemingway C, Freeman JM, Pillas DJ, Pyzik PL. *Pediatrics*. 2001;108:898–905.

Recent studies have demonstrated that the diet may not require a fasting phase at initiation and may be initiated either with full calories[20,21] or without an admission to the hospital.[22,23] However, many centers still use at least some fasting periods because of the occasional immediate benefits seen for some children. We have observed a dramatic effect of fasting similar to a "loading" dose of intravenous anticonvulsant agents.[24] Most centers still admit children to observe their initial response to the diet and possible immediate adverse effects.

TABLE 2 **Factors Involved in KD Initiation and Maintenance, With Changes Described**

Diet Factor	Management	Comment
Diet initiation		
1950s	Admission and fasting until the child had lost 10% of body weight and had urinary ketones of 160 mg/dL	
1960s–1990s	Admission and fasting 48 h	
Current	Johns Hopkins: admission and fasting 24 h ± ketosis, calories gradually increased; other centers have demonstrated efficacy without a fast and with full calories immediately; most centers still admit for education and immediate adverse-effect monitoring	Value of admission and fasting unproven; Atkins and low glycemic index treatment studies do neither
Modified Atkins diet and low glycemic index under study, both 1:1 ratio diets		
Old	3:1 infants and adolescents 4:1 other children	
Current	Generally still the same Atkins diet under study, probably 2:1 Boston: low glycemic index treatment even lower	Many countries in Asia use lower ratios
Fluids		
Old	Tight restriction to 80% daily requirement	Most children before the diet were drinking less fluids than either the daily requirement or the diet allotment
Current	Unclear if fluid restriction is necessary	May be helpful to prevent kidney stones by giving ad lib
Calories		
Old	Tight restriction to 75% daily requirement, with modifications made afterward	
Current	Variable on the basis of estimated needs	Animal, not human, studies demonstrate benefit to caloric restriction
Carbohydrates		
Old	<10 g/d	
Current	Unclear maximum amount	Atkins studies show that 20 g/d may be efficacious
Ketones		
Old	≥3 to ≥4 (80–160 mg/dL) urine ketones, checked frequently, believed crucial for seizure control	
Current	Necessary level and even importance unclear	Interest in alternative methods of measurement (breath and serum)
Duration of diet (maximum)		
Old	2 y	
Current	As long as it is helpful	Some evidence for patients with infantile spasms suggests that short periods (eg, 6 mo) may be sufficient

Alternative KDs

The medium-chain triglycerides (MCTs) diet uses fat sources that are more ketogenic than the saturated long-chain triglycerides (LCTs) typically consumed in the traditional KD, thus allowing more carbohydrates to be incorporated into the diet.[25–27] A trial comparing the MCT diet, classic LCT diet, and a modification of the 2 (the Radcliff diet) found they were of roughly equal efficacy, but the MCT diet had a higher incidence of abdominal cramps, diarrhea, nausea, and vomiting.[27] Occasionally we add small quantities of MCT oil to the classic KD to alleviate constipation and dyslipidemia. An ongoing trial is investigating the LCT and MCT diets in a randomized manner (J. H. Cross, MD, personal communication, 2006).

A modified Atkins diet also is emerging as a possible alternative dietary treatment for seizures.[28,29] With restriction of carbohydrates (10–20 g per day), the Atkins diet can induce ketosis and does not restrict protein, fluid, or calories and does not require an admission or a fast. In a follow-up study, 65% of patients on the Atkins diet had a >50% reduction in seizures and 6 (35%) had a >90% reduction.[29] Additional studies of the modified Atkins diet are underway including adult patients with epilepsy.

A third diet is the low glycemic index diet,[30] in which fruits, breads, and starches are discouraged. This diet has even fewer carbohydrate restrictions than the modified Atkins diet.

Who Are the Best Candidates for the Diet?

The efficacy of the diet is independent of the type of seizure and is effective for both generalized and partial seizures[13] at varied ages.[31–35] Some refractory disorders that respond to the diet include Dravet syndrome,[36] myoclonic-astatic epilepsy,[37–39] Rett syndrome,[40,41] migrational disorders,[42] and tuberous sclerosis complex.[43,44] The KD may be particularly helpful in the treatment of infantile spasms, especially when used earlier in the course of the disorder.[31,45] Formula-based diets, whether fed via bottle or gastrostomy tube, have shown improved compliance as well as efficacy.[46,47] Although no one particular anticonvulsant medication has been described as specifically beneficial in combination with the diet, the use of the diet in combination with vagus nerve stimulation may be synergistic.[48]

Patients with partial-onset (focal) seizures seem less likely to either improve significantly or become permanently seizure free.[49,50] Children with a demonstrated, surgically approachable focus may respond to the diet but have less likelihood of either >90% seizure reduction or actual seizure freedom (unpublished data). In a limited case series, Lafora body disease did not respond well to the diet.[51]

Mechanisms of Action of the Diet

The mechanism(s) through which the KD exerts its anticonvulsant effects remains elusive. Although there is an abundance of data regarding the physiologic effects a KD exerts on humans and rodents, how these effects contribute to seizure protection is unclear. The diet has both anticonvulsant (ie, stopping a discrete seizure) properties and antiepileptic (ie, stopping the propensity to develop recurrent unprovoked seizures, or epilepsy) effects. The latter is suggested by series that examined the diet's potential disease-modifying effects in patients who discontinued the diet, sometimes after only months, yet still enjoyed long-term freedom from seizures.[14,52]

Anticonvulsant effects of the KD have been studied primarily in models of nonepileptic rodents receiving a KD and later exposed to proconvulsant agents or electrical stimuli (eg, pentylenetetrazol, maximal electroshock).[53,54] Studies in mice that examined changes in glutamate (eg, the primary central nervous system excitatory neurotransmitter) and γ-aminobutyric acid (GABA) (eg, the primary central nervous system inhibitory neurotransmitter) suggested a key role for the KD in protection from seizures.[55] Although actual levels of these neurotransmitters may not be elevated, there is a suggestion that flux through the GABA shunt may be increased, thus favoring inhibition of aberrant neuronal firing.[56] Changes in levels of GABA (measured by magnetic resonance spectroscopy) and other cerebrospinal fluid amino acids have been documented in patients on the KD, which suggests that they may play a role in seizure protection.[57,58]

Changes in mitochondrial biogenesis (eg, increased metabolic enzymes and mitochondrial number) also have been documented, reviving an old hypothesis that changes in cellular metabolism may modify the cellular milieu into a less hyperexcitable (and hence, less epileptiform) state.[54,59] Early work on the KD suggested that ketone bodies, especially β-hydroxybutyrate, might be anticonvulsant.[25] Subsequent in vitro work argued against this idea, but acetone (another ketone body), initially believed to be unimportant because of its volatility, has anticonvulsant properties.[60–62]

The KD may also have antiepileptic effects. One speculation is that the antiepileptic effect is exerted via neuroprotection, but the mechanism for this is unclear. Neuroprotection may involve either protection from free oxygen radicals or prevention of apoptosis. Protection from free radicals may be provided via a decrease in coenzyme Q semiquinone,[63] elevated mitochondrial uncoupling proteins, or elevated glutathione peroxidase. Uncoupling proteins, shown to be induced in mice that consume a KD, dissipate the mitochondrial membrane potential, thus protecting against free radical damage.[64] The mechanism of this induction might be via fatty acids, which are elevated in the serum of patients on the

KD.[42,65] The KD also induces glutathione peroxidase, which subsequently prevents damage to the cell membrane caused by lipid peroxidation.[66] The KD may protect against apoptosis via increased levels of the protective protein calbindin or prevention of the accumulation of the pro–cell-death protein clusterin.[67,68] Very recent work has shown the role of 2-deoxyglucose, an inhibitor of glycolysis, in protection from seizures.[69] Reports of its anticonvulsant and antiepileptic properties suggest that there may be antiglycolytic compounds which may possibly mimic some of the mechanisms of action of the KD and constitute a new class of drugs for treating epilepsy. Additional investigations into the mechanism(s) of action of the KD may lead to answers not only as to why it works but also what may cause seizures and epilepsy to develop.

Adverse Effects of the Diet

Adverse effects of the KD only infrequently require the diet to be discontinued but are important for neurologists and pediatricians to recognize. Early-onset adverse effects associated with diet initiation include acidosis, hypoglycemia, gastrointestinal distress, dehydration, and lethargy. They are typically transient and easily managed and are minimized if patients are not fasted. Later adverse effects include dyslipidemia, kidney stones, and slowing of growth.

Cholesterol and lipids are adversely affected on the diet. The most extensive study of dyslipidemia on the diet followed 141 children prospectively over 2 years.[70] In these children, there was an increase in atherogenic apoB-containing lipoproteins very low-density lipoprotein and low-density lipoprotein and a decrease in the antiatherogenic high-density lipoprotein cholesterol. Cholesterol increased ~130% but then stabilized over the 2-year period. It is interesting to note that the lipid profiles of children on the KD >6 years returned toward baseline.[71] The long-term effects of these changes in lipids, if any, are unknown, but it should be recalled that most patients remain on the diet for only 2 years and then return to a diet with normal fat ingestion.

Kidney stones occur in 5% of children on the KD and is thought to be secondary to a combination of acidosis, urine acidification, hypercalciuria, and hypocitraturia.[72] Although anticonvulsant agents with carbonic anhydrase-inhibition properties (topiramate and zonisamide) have an independent risk of stones, the combined prevalence with the diet was not higher than either therapy alone.[73] The risk of stones has significantly decreased since the prophylactic use of oral potassium citrate (Polycitra K) to alkalinize the urine.[74]

Children on the diet grow normally, but the growth of younger children seems to be slowed more than that of older children.[75] Those on the diet for >6 years were typically in the <10th percentile for height and weight.[71] Growth seems to increase rapidly after diet discontinuation.[76] Children on the KD are monitored carefully and regularly by a registered dietitian for weight and height slowing.

Bone density may be decreased by the KD. A higher risk of skeletal fractures in children on the KD has been reported.[71,77,78] Prevention with calcium supplementation, pamidronate, or lower KD ratios remain unproven.

Deaths have been reported in patients on the diet, although it is unclear that any of the deaths have been a result of the diet.

It is clear that the success and safety of the diet are best achieved by the close supervision of the patient by an experienced team that includes the physician, the dietician, and, often, a nurse.

Other Uses Beyond Epilepsy

Multiple uses of the KD are being investigated. All reported studies to date are very preliminary but are discussed in this review to indicate possible future uses of the diet. Neurodegenerative disorders provide a unique opportunity to study cellular protection via dietary means. In fact, the mechanism of the KD in neuroprotection might be more straightforward than its mechanism of protection against seizures.

Parkinson disease may be partly attributable to dysfunction of mitochondrial complex I.[79] The KD, which effectively bypasses the requirement for complex I, may provide an alternative pathway for normal cellular metabolism. This notion served as the rationale for a case series that showed some improvement in clinical rating scales in 7 adults with Parkinson disease who consumed a KD for 28 days.[80] Although the hypothesis that bypassing complex I is an attractive one, it is possible that lower dietary protein levels and weight loss in patients on the diet simply improved the patients' baseline levodopa pharmacokinetics.[81]

A KD reduced amyloid-β 40 and 42 in a mouse model of Alzheimer disease.[82] Administration of a KD for 43 days was associated with a decrease in the amount of total brain amyloid-β content, although performance on an object-recognition task was unchanged. The KD also was associated with delayed progressive motor neuron loss and improved performance on a motor task (compared with controls) in a transgenic mouse model of amyotrophic lateral sclerosis, with in vitro data again showing a protective effect of β-hydroxybutyrate.[83] The KD was associated with decreased cortical contusion volumes 7 days after a standardized controlled cortical impact in rats of specific pediatric ages.[84] A key role for ketone bodies was suggested in a study that showed improved adenosine triphosphate production in the same trauma model after an infusion of β-hydroxybutyrate.[85]

The KD has been reported to have decreased tumor size in 2 patients with astrocytomas[86] and recently has been shown to inhibit brain tumor growth in a mouse model of an astrocytoma.[87] Ketosis may also improve

migraine headaches in a manner similar to the beneficial preventive effect of many anticonvulsant drugs.[88] The Atkins diet has been reportedly effective for narcolepsy in a small case series, as well.[89]

Psychiatric disorders have also been treated with the KD. Recent studies have demonstrated its use for autism and depression.[90,91] The mechanism of action of the KD for psychiatric disorders is unclear.

In addition, the diet may have uses beyond neurologic disorders. Very preliminary studies indicate that the KD may be useful in conditions that involve an imbalance of glucose metabolism, including type 2 diabetes mellitus and polycystic ovary syndrome.[92,93] The diet has been described for use in hypercholesterolemia.[94]

CONCLUSIONS

The past decade has been an amazing one for those interested in the KD. Its increasing use in children with difficult-to-control seizures has opened new vistas for these children and also for our understanding of epilepsy. Its potential use in adults by using a less restrictive Atkins diet may make a difference to this population as well. The diet's documented efficacy and tolerability have opened new horizons as it is tried for a variety of ills from brain tumors to migraine, and from head trauma to neurodegenerative diseases. Most exciting is the realization that beliefs concerning a high-fat diet making people fat and dyslipidemic have been proven false. Researchers are rediscovering that ketone bodies are not necessarily bad and that glucose is not necessarily good. A whole new era of metabolic research has opened up. It is not completely clear where it will lead, but its promise is exciting.

ACKNOWLEDGMENT

Dr Hartman was supported by the Epilepsy Foundation through the generous support of Pfizer, Inc.

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MOST STUDENTS IN BIG CITIES LAG BADLY IN BASIC SCIENCE

"At least half of eighth graders tested in science failed to demonstrate even a basic understanding of it in 9 of 10 major cities, and fourth graders, the only other group tested, fared little better, according to results released here Wednesday. The outcome of those tests, part of the National Assessment of Educational Progress, often called the nation's report card, showed that student performance in urban public schools was not only poor but also far short of science scores in the nation as a whole."

Schemo DJ. *New York Times*. November 15, 2006
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Pediatrics 2007;119;535
DOI: 10.1542/peds.2006-2447