State of the Ketogenic Diet(s) in Epilepsy

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Fasting has been recognized as a treatment for seizures since ancient times. The ketogenic diet is a low-carbohydrate, adequate-protein, high-fat diet that biochemically mimics the fasting state and has been used to successfully treat seizures for 85 years. The diet has enjoyed a resurgence in popularity over the past decade and is gaining acceptance and use worldwide. Many studies over the past several years have explored possible mechanisms of action for the ketogenic diet. This review addresses these studies, as well as recent research regarding possible indications for the diet, variations in its initiation, side effect profiles, and the recent use of modified formulations to improve tolerability.

Introduction

The ketogenic diet (KD) is a high-fat, moderate-protein, low-carbohydrate diet used to treat intractable epilepsy, primarily in the pediatric population. The recognition that dietary restriction could treat epilepsy dates back to ancient times. Hippocrates provides one of the earliest records of this in his prescription of fasting for an epileptic patient in order to purge the body of polluted humors [1]. Fasting as a treatment for epilepsy is also mentioned in the Bible when Jesus is brought an adult with childhood-onset epilepsy and declares, "this kind does not leave but by prayer and fasting" (Matthew 17:14-21). Modern use of fasting gained acceptance in 1911 in France, when case reports documented the efficacy of occasional weeks of fasting for treatment of seizures [1–3]. By the 1920s in the United States, fasting was replaced with a high-fat, low-carbohydrate, calorie-restricted diet created intentionally to mimic the ketosis created by the body during a starvation state [1–3]. This first KD became a popular treatment for children and adults with epilepsy until the introduction of anticonvulsant drugs, beginning with diphenylhydantoin in 1938. A resurgence of the diet occurred in 1994 when a young boy from California with epilepsy intractable to anticonvulsant drugs and a corpus callosotomy was successfully treated with the KD at the Johns Hopkins Institution in Baltimore, and his father created the Charlie Foundation to promote its use [4].

Today, the KD is used to treat intractable epilepsies in all age groups and is gaining popularity worldwide, with many centers having started their own programs in just the past decade [5•]. The classic KD is a 4:1 or 3:1 ratio of fat to combined protein and carbohydrate, and is individually tailored to typically provide 75% to 80% of the recommended daily allowance of calories and 80% of estimated daily allowance of fluids. At many institutions, including ours, this fluid and calorie restriction is less commonly utilized. The diet mimics a starvation state by shifting the main source of energy from carbohydrate to fat, although the exact mechanism of its efficacy is a subject of ongoing research. This review addresses the indications, mechanisms, methods of initiation, alternative formulations, and known side effects of the KD to date, with an emphasis on research from the past several years specifically.

Indications

Significant research in the past several years has attempted to determine what seizure types and syndromes respond best to the ketogenic diet. In large studies, the efficacy of the diet is independent of the type of seizure and has been effective for both generalized and partial seizures [6,7]. A typical patient is 5 to 10 years of age with a mixed epilepsy syndrome such as Lennox-Gastaut syndrome, although recent studies have demonstrated efficacy in infants, adolescents, and adults [8–10]. Additional research has demonstrated efficacy in notoriously refractory disorders such as Dravet syndrome, myoclonic-astatic epilepsy, and tuberous sclerosis complex [11–13].

Recent evidence suggests that the KD may be particularly helpful in the treatment of infantile spasms. A retrospective study of 23 infants with mostly intractable spasms demonstrated greater than 90% improvement in approximately half of the patients over a 3- to 12-month period [14•]. Interestingly, success of the KD in this cohort may be due in part to an infant's primary dependency on an all-liquid KD. Studies that have evaluated formula-based administration, whether fed via bottle or gastrostomy tube, indicate better compliance and ultimately better seizure control compared with the typical solid-food diet [15,16]. In recent years, many

Table 1. Proposed mechanisms of action for the ketogenic diet

Increased synthesis of γ-aminobutyric acid
Direct action of ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone)
Acidosis
Dehydration
Direct action of fatty acids/polyunsaturated fatty acids
Altered energy state
Caloric restriction
Neuroprotection
Neurosteroid modulation
Mitochondrial uncoupling proteins
Glucose stabilization
Body mass index stabilization
Brain alanine release
Increased nitric oxide levels in the hippocampus

KD centers have found that dependency on gastrostomy tubes, regardless of age, may represent a special indication for the KD in patients with otherwise intractable seizures or intolerable side effects to anticonvulsant drugs.

Certain metabolic disorders can also be a special indication for the KD. Pyruvate dehydrogenase deficiency is an inherited mitochondrial disease in which patients are unable to oxidize glucose and consequently are dependent on ketone bodies as an energy substrate [17]. Similarly, patients with glucose transporter protein deficiency (GLUT-1) cannot utilize carbohydrate as an effective fuel source and are dependent on ketone bodies [18]. In both of these disorders, the KD can provide an alternative fuel source and treat associated seizures. It is also important to recognize that there are metabolic disorders that are contraindications to the KD. Such disorders involve problems with the metabolism of a high-fat diet and include pyruvate carboxylase deficiency, carnitine deficiencies, fatty acid oxidation defects, and possibly some mitochondrial disorders.

Efficacy

Historical recognition that dietary restriction could treat seizures makes the KD unique in that clinical studies reporting its efficacy predate animal models. In the largest prospective study to date of 150 children, 26% had a 50% to 90% reduction in seizures, an additional 31% had a more than 90% reduction, and another 3% were seizure free at 3 months [6]. A recent meta-analysis of studies from 1925 to 1998 reports that 30% of patients have a 50% to 90% reduction in seizures and an additional 37% of patients have more than a 90% reduction in seizures [19].

Despite a large number of mostly retrospective studies demonstrating its efficacy, the diet has never been proven in a randomized, controlled manner [20••]. This appears to be changing. Studies are in various stages of analysis at Great Ormond Street Hospital in London (Personal communication, H. Cross) and Johns Hopkins Hospital in Baltimore that do employ a randomized, controlled protocol. For purposes of patient counseling, it is reasonable to state that approximately one third of patients will have greater than 90% reduction in seizures, one third will have a 50% to 90% reduction, and one third will have less than a 50% reduction [21]. The success of the KD is at least as good, if not better, than the newer-generation anticonvulsants for refractory epilepsy [22•].

Mechanisms of Action

The mechanism of action for the success of the KD is presumed to be multifactorial and is the subject of ongoing research. The KD shifts the main energy source of the brain from glucose to fat and myriad metabolic changes occur, even during the fasting period. When the body is deprived of carbohydrate, it is forced to metabolize fatty acids. The brain does not oxidize fatty acids and instead is dependent on the formation of ketone bodies in the liver, which are then transported across the blood-brain barrier by special transporters known as monocarboxylic acid transporters [23]. The major ketone bodies are β-hydroxybutyrate, acetoacetate, and its byproduct acetone. In starvation states, as mimicked by the KD, ketone bodies provide at least 60% of the brain's energy requirement [23]. They are also important components of lipid synthesis, including myelin, and contribute to normal myelination and development of the central nervous system [23]. Early theories regarding mechanism of action focused on the role of ketone bodies, although newer studies have expanded our understanding of molecular changes induced by the diet and their potential role in controlling seizures (Table 1). Such studies make up a large percentage of recent publications regarding the KD. These studies and theories are discussed briefly in the following text, although the reader is referred to individual publications for further detail.

Ketone bodies and ketosis

It has long been hypothesized that ketosis was the major mechanism of action of the KD. All three ketone bodies are increased in serum and cerebrospinal fluid of individuals on the KD. Acetone suppresses seizures in animal models of tonic-clonic, typical and atypical absence, and complex partial seizures [24]. Acetoacetate has been shown to be neuroprotective against the excitatory neurotransmitter glutamate, which is believed to have a role in provoking seizures as well as contributing to neurodegeneration in intractable epilepsies [25,26•]. Finally, β-hydroxybutyrate is structurally similar

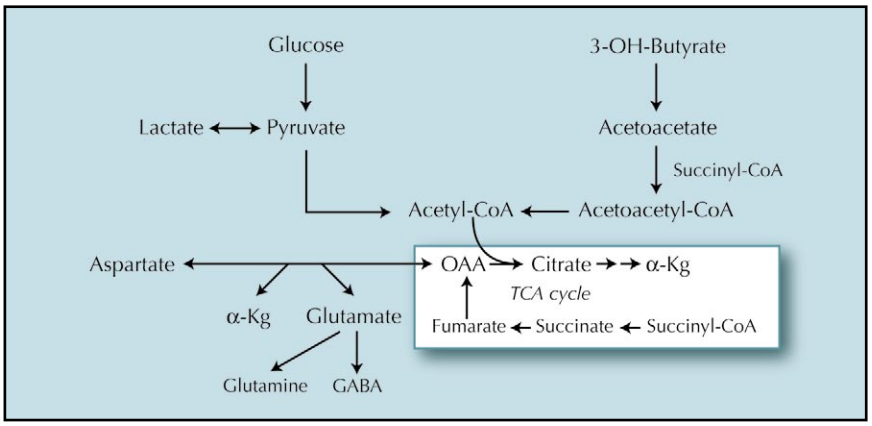

Figure 1. Example of glutamate metabolism. α-Kg—α-ketoglutarate; CoA—coenzyme A; GABA—γ-aminobutyric acid; TCA—tricarboxylic acid. (*Adapted from* Yudkoff et al. [26•]; with permission.)

to γ-aminobutyric acid (GABA), a key inhibitory neurotransmitter and potent anticonvulsant [23].

The level of GABA is affected by the ketotic state in a way that is advantageous for seizure control. In the shift from glycolysis to fatty acid metabolism, ketosis forces the consumption of oxaloacetate (OAA), a tricarboxylic acid cycle substrate. In a fed state, OAA is used to synthesize the excitatory neurotransmitters glutamate and aspartate. When OAA is consumed in the ketotic state, however, glutamate is shunted to GABA synthesis, ultimately making more of this inhibitory neurotransmitter and less of the excitatory neurotransmitters (Fig. 1) [26•].

Acidosis and dehydration

Most patients on the KD develop a baseline acidosis with serum bicarbonate ranging from 12 to 18 mg/dL. Despite a chronic acidosis, patients compensate as demonstrated by normal blood pH. Literature reviews have failed to find isolated altered brain pH as a possible mechanism of action, although it has recently been suggested that changes in ionic gradients and cellular mechanisms to maintain a normal pH may have an anticonvulsant effect rather than the absolute pH [27•].

Acidosis is typically associated with dehydration and the concomitant removal of extracellular fluid. As cellular swelling can cause the neuronal synchrony and recruitment required of seizure propagation, it was thought that dehydration might prevent cellular swelling and prove to be anticonvulsant, but again, reviews of studies of water and electrolyte shifts fail to reach such a consensus [27•]. Anecdotally, most patients seem to have no change in seizure control with increased fluids or oral alkalinization, which can improve acidosis.

Change in lipids

It is no surprise that lipid levels change when consuming a diet primarily composed of fat. Although there is no irrefutable evidence that higher lipid levels correspond to improved seizure control [2,22•], the potential role of fatty acids has become increasingly complex in recent years. Fats consumed in the KD are primarily saturated, but the synthesis of polyunsaturated fatty acids (PUFAs) increases on the KD and may provide a novel anticonvulsant mechanism. Specifically, PUFAs modulate the excitability of neurons by inhibiting voltage-gated sodium channels, similar to the mechanism of action of antiepileptics such as phenytoin [28]. It is also now understood that fatty acids act like hormones for specific cell receptors, which ultimately affect cellular metabolic pathways and expression of genes responsible for neurotransmitter synthesis. In the brain, PUFAs act as ligands for peroxisome proliferator activated receptor α (PPARα) on astrocytes, which drives the expression of key ketogenic enzymes. This has a major effect on the intermediary metabolism of amino acids and is proposed to alter the expression of excitatory versus inhibitory neurotransmitter synthesis in proportions that favor seizure control [29]. This theory is supported by a study analyzing the cerebrospinal fluid levels of excitatory and inhibitory amino acids in children before and after induction of the ketogenic diet [30].

Additionally, it has been discovered that PUFAs activate a distinct family of potassium channels that modulate cell membrane hyperpolarization and reduce cell excitability [27•]. Valproic acid, a short branch chain fatty acid, activates PPARα and presumably shares these mechanisms of action.

Altered energy state

Intuitively, one may expect that in the fasting state, less adenosine triphosphate (ATP) is made and overall there is a lower energy state in the brain. Animal models demonstrate the opposite, however. Ketosis induces a relative increase in the ATP/adenosine diphosphate ratio, favoring an increase in "energy charge" [22•]. Although seizures are an energy-consuming process requiring ATP, reviews of this theory propose that there is a basal increase in ATP-dependent processes, such as activation of sodium pumps, leading to cellular hyperpolarization, and increased glutamate uptake from the extracellular space by astrocytes, decreasing the availability of this excitatory neurotransmitter needed for seizures [2,23,26•].

Related to the change in energy state is the potential role of insulin levels. Decreased levels of insulin, as seen in the fasted state, are known to reduce norepinephrine and increase dopamine activity, which can increase the seizure threshold [31]. However, insulin has also been reported to increase GABA receptors, decrease cell excitability in a seizure-protective fashion, and open ATP-sensitive potassium channels, ultimately causing membrane hyperpolarization [27•]. In summary, the role of insulin remains complex and incompletely understood.

Neurosteroids

Evidence is accumulating for the role of neurosteroids as endogenous anticonvulsants. Unlike typical endocrine hormones, neurosteroids do not have nuclear hormone receptors affecting downstream transcription of genes, but rather act on membrane-bound receptors to alter central nervous system function [32]. Research in this area demonstrates that neurosteroids modulate the activity of ion channels on GABA receptors, altering seizure susceptibility. In a recent study of rats on the KD, plasma levels of the neuroactive steroid pregnane and androstane-class neurosteroids decreased, suggesting a role for the KD in this regard [33•].

Caloric restriction

The health benefits of caloric restriction are well documented in animal studies and include slowed aging, less disease, and extended longevity. The classic KD uses caloric restriction, and errors in initiating and maintaining the diet often relate to violation of this tenet secondary to overestimation of caloric needs or weight gain. Indeed, poorer seizure control has been reported in mice with KD administered ad libitum compared with KD with caloric restriction [34•]. Two recent animal studies support caloric restriction as an independent mechanism of action in seizure control. Bough et al. [35] compared field potentials recorded in vivo from the dentate gyrus in rats fed one of three diets: ketogenic caloric restricted (KCR), normal caloric restricted (NCR), or normal ad libitum. Both the KCR-fed and NCR-fed rats demonstrated anticonvulsant mechanisms as measured by tissue excitability. Only the KCR-fed rats, however, demonstrated an antiepileptogenic effect when exposed to a kindling-like phenomenon. The conclusion was that caloric restriction in itself may be the mechanism of action for the anticonvulsant properties of the KD.

A second study, by Greene et al. [34•], supports a role for caloric restriction as having both anticonvulsant and antiepileptogenic properties. In this study, juvenile and adult mice were fed one of three diets: ad libitum, a 15% caloric restriction (juvenile and adult mice), or a 30% caloric restriction diet (adult mice only). All mice were subject to measurements of seizure susceptibility induced by human handling. In accordance with caloric-restriction data, the calorie-restricted mice were noted to be more healthy and active than the ad libitum mice. All calorie-restricted mice demonstrated a reduced incidence (anticonvulsant) and delay in the onset of seizures (antiepileptogenic) compared with the ad libitum mice. This effect was dose dependent in that the 30% calorie-restricted mice had greater reduction in seizures and longer delay in onset of seizures. Interestingly, when the authors compared their results with the same parameters in mice fed the KD, the juvenile 15% calorie-restriction diet was more effective than the KD [34•].

Other effects

In addition to anticonvulsant and antiepileptogenic properties, the KD may offer neuroprotective effects. Seizures are known to induce the formation of injurious reactive oxygen species (ROS). In mice, the production of ROS is diminished by increasing the expression of mitochondrial uncoupling proteins [36], and in rat hippocampi increased activity of the neuroprotective enzyme glutathione peroxidase also serves to protect the cortex from ROS [37]. S100B, a key excitatory cytokine secreted by astrocytes and found in increased concentration in the temporal lobes of patients with intractable epilepsy, is lowered in the cerebrospinal fluid of rats after being fed the KD, offering yet another potential neuroprotective effect of the KD [38].

Initiation of Diet and the Role of Fasting

The KD requires attention to detail and a daily commitment to limited food choices, all of which must be carefully weighed and recorded. Typically, initiation of the diet is done in the hospital and entails a 24- to 48-hour fast before the introduction of the KD foods or formula. The Johns Hopkins protocol (Table 2) is widely used, although recent studies have altered this protocol to an outpatient setting or to eliminate fasting.

In a retrospective review of 54 patients undergoing initiation of the KD, 37 were initiated as outpatients and 17 as inpatients [39]. Furthermore, the majority of these patients did not undergo an initial fast. Sixty-two percent of the outpatients and 71% of the inpatients reported more than a 50% reduction in seizures, which is comparable to the results with traditional inpatient approach. Additional studies also demonstrate that initial fasting makes no difference in the ultimate efficacy of the diet [40•,41,42••]. A recent prospective, randomized study of a fasting versus gradual initiation by Bergqvist et al. [43••] observed no difference in 3-month outcomes and fewer side effects with a gradual approach.

Benefits of inpatient hospitalization include the opportunity for education, monitoring of patients for tolerability and acute worsening as ketosis develops, and the chance for families to establish rapport with one another. Additionally, some patients demonstrate an impressive and immediate response with initial fasting

Table 2. Johns Hopkins Hospital protocol for initiation of the ketogenic diet

Day prior to admission (Sunday)
Reduced carbohydrates for 24 hours
Fasting starts the evening before admission with clear no-carbohydrate fluids only
Day 1 (Monday)
Admitted to the hospital at 12 noon
Fasting continues
Fluids restricted to 60–75 cm^3/kg
Blood glucose monitored every 6 hours
Basic laboratory results obtained if not done previously (metabolic profile, urine calcium, urine creatinine, fasting lipid profile, anticonvulsant levels)
Change to carbohydrate-free medications
Parents begin educational program (diet overview)
Day 2 (Tuesday)
Dinner, given as "eggnog," providing 1/3 of calculated maintenance dinner calorie allowance
Blood glucose checks discontinued after dinner
Parents begin to check urine ketones periodically
Education continues (calculating and weighing foods)
Day 3 (Wednesday)
Breakfast and lunch given as "eggnog," providing 1/3 of maintenance breakfast and lunch calorie allowance
Dinner (still "eggnog"), increased to 2/3 of maintenance dinner calorie allowance
Education continues (maintenance, checking ketosis)
Day 4 (Thursday)
Breakfast and lunch given as 2/3 of maintenance meal allowance
Dinner is first full ketogenic meal (not "eggnog")
Education completed (handling illnesses)
Day 5 (Friday)
Full ketogenic diet breakfast (calories) given
Prescriptions reviewed and follow-up arranged
Child discharged to home

in the hospital, which can be utilized therapeutically again when they are outpatients during periods of seizure exacerbations [44]. Many centers are now individualizing their approach to the start of the diet based on each patient.

Alternative Formulations

Medium chain triglyceride oil diet

The KD has changed little in the 85 years since its introduction. Because it can be time consuming and restrictive, there has been considerable interest in alternative formulations to minimize these negative characteristics and maximize compliance. One of the first was a diet based on medium chain triglycerides (MCT) rather than the saturated long chain triglycerides (LCT) typically consumed in the traditional KD [45]. In the late 1960s, it was discovered that MCTs were more ketogenic than LCTs. By substituting MCT oil for foods rich in LCT, patients could enjoy more liberal consumption of carbohydrates and protein while maintaining ketosis. Indeed, the MCT diet was considered easier to prepare and was better accepted by the first study participants. Seizure efficacy was comparable with the KD, with 50% of patients demonstrating a "…therapeutically significant anticonvulsant effect…" within days of diet initiation [45]. Unfortunately, because MCT oil is rapidly absorbed by the gastrointestinal tract, it is often associated with symptoms including abdominal cramps, diarrhea, nausea, and vomiting that ultimately made it used only in a few centers [1]. Occasionally, it is added in small quantities to the classic KD to alleviate constipation and dyslipidemia. An ongoing trial is underway in London investigating the two diets in a randomized manner (H. Cross, Personal communication).

Table 3. Modified Atkins diet protocol

Copy of *Dr. Atkins' New Diet Revolution* and a carbohydrate counting guide provided
Carbohydrates described in detail and restricted to 10 g/d for the first month (increase afterwards if child and family desire)
Fats (eg, 36% heavy whipping cream, oils, butter, mayonnaise) encouraged
Clear, carbohydrate-free fluids not restricted
Low-carbohydrate multivitamin and calcium supplementation prescribed
Check urine ketones semiweekly and weight weekly
Medications left unchanged for at least the first month, but changed if necessary to tablet or sprinkle (nonliquid) preparations
Low-carbohydrate, store-bought products (eg, shakes, candy bars, baking mixes) discouraged for at least the first month
Complete blood count, complete metabolic profile (SMA-20), urine calcium and urine creatinine, urinalysis, and fasting lipid profile at baseline, 3 months, and 6 months

Corn oil diet

In addition to gastrointestinal distress, MCT oil was notoriously expensive and could be difficult to obtain. In the 1980s, corn oil was introduced as an economic, widely available substitute for MCT oil. In a study of six patients who achieved greater than 90% reduction in seizures on an MCT-based KD, all were successfully transitioned to corn oil without loss of seizure efficacy and five were able to reduce or discontinue anticonvulsant drugs [46].

Modified Atkins diet

In the past 2 years, a modified Atkins diet has emerged as a viable dietary treatment for seizures [47,48•]. With sufficient restriction of carbohydrates (10–20 g/d), the Atkins diet can induce ketosis and does not restrict protein, fluid, or calories, nor does it require an admission or a fast (Table 3). Atkins-friendly meals are available in restaurants and grocery stores, making the diet more accessible and versatile compared with the classic KD, without the need to measure and weigh foods. A small study of six patients aged 7 to 52 years tested the efficacy of the Atkins diet for intractable epilepsy [47]. Five maintained at least moderate ketosis and half achieved greater than 90% reduction in seizures. Interestingly, the level of ketosis seemed to correlate with success.

In a follow-up study of 20 children started prospectively on the modified Atkins diet with initially 10 g/d of carbohydrate, 13 (65%) had greater than 50% reduction in seizures and six (35%) had greater than 90% reduction [48•]. Large urinary ketosis was attained within four days in all children, although tended to trend downwards over time. Approximately one third still found the diet restrictive, and increasing carbohydrates to 15 to 20 g/d was generally helpful without reducing efficacy. Nine children were able to reduce anticonvulsants. Blood urea nitrogen (BUN) increased significantly, although creatinine remained unchanged, and total cholesterol trended upwards from 192 to 221 mg/dL ($P = 0.06$) [48•]. Weight loss was infrequent, and 13 children actually gained weight over the 6-month study period. Further studies of this modification to the KD are underway at our institution.

PUFA supplementation

Another potential dietary formulation is oral supplementation with PUFAs. As discussed previously, PUFAs have demonstrated anticonvulsant and neuroprotective properties. A single study of five patients provided a PUFA supplement in the form of an omega-3 bread spread each morning for 6 months demonstrated a reduction in seizures from 1 to 14 per week before the supplement to 0 to 1 per month after the supplement [49]. A recent randomized, double-blind study from England of 58 adults with epilepsy found a reduction in seizures at 6 weeks, but a return to baseline at 12 weeks [50].

Low-glycemic index diet

Finally, there is some evidence for the efficacy of low-glycemic index diets [51]. A group at Massachusetts General Hospital has recently described a diet that, although still relatively high in fats, usually allows 40 to 60 g of low-glycemic (glycemic index < 50) carbohydrates, and calories are only roughly controlled. In a study of 20 patients aged 5 to 34 years, 50% had a greater than 90% reduction in seizures, and an additional 25% had a 50% to 90% improvement [51]. The mechanism by which this diet works is not clear, and may involve low-level ketosis, serum glucose stabilization, or another mechanism not yet determined.

Side Effects

Overview

In general, side effects of the KD have been well studied and rarely lead to morbidity or mortality (Table 4). There are early-onset side effects associated with diet initiation including acidosis, hypoglycemia, gastrointestinal distress, dehydration, and lethargy. Some of these are minimized if patients are not fasted and all are typically transient and easily managed without the need for diet discontinuation [42••].

It is presumed that the longer patients stay on the diet, the more likely they are to experience late-onset side effects. Some of these are common and even expected, including lack of weight gain and constipation if on the

classic diet or gastrointestinal distress if on the MCT diet. More concerning, but less common, are changes in lipid profiles, development of kidney stones, and growth retardation. Blood and urine tests are periodically followed to monitor for development of these complications.

Dyslipidemia

The most extensive study to date analyzing changes in lipid profiles is a 2-year prospective study of 141 children initiated on the KD [52•]. Results revealed significant increases in the atherogenic apolipoprotein B–containing lipoproteins very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) and a decrease in the antiatherogenic high-density lipoprotein (HDL). Whether these changes lead to chronic atherosclerosis is unknown, but it appears doubtful given that most children discontinue the KD within 2 years. Long-term studies of children on the KD more than 6 years indicate lipid profiles may return to baseline, a trend noticed at 2 years in the previous study [53].

Kidney stones

There is an approximate 5% to 6% risk of developing kidney stones while on the ketogenic diet, thought to be secondary to chronic acidosis, urine acidification, hypercalciuria, and hypocitraturia [54•]. The use of oral potassium citrate (Polycitra K) to alkalinize the urine has been discussed, but not proven [54•]. Theoretically, the risk of kidney stones could increase with concomitant use of anticonvulsants with carbonic anhydrase–inhibiting properties (topiramate and zonisamide); however, a recent study showed no increased risk [55].

Growth

Several studies have investigated the impact the KD has on growth [56,57•,58]. In all studies weight decreased, as expected. Height was initially maintained, but the longer patients stayed on the diet and the younger they were, the more at risk they were for not growing along their height percentiles [56]. This appears to persist in children on the diet for over 6 years, with nearly all children less than 10th percentile for height and weight [53]. Somewhat reassuring, however, is the indication that after the KD is stopped, there appears to be catch-up growth to baseline [58].

Table 4. Potential side effects of the ketogenic diet

Common
Lack of weight gain
Constipation
Hypoglycemia (with fasting)
Occasional
Gastrointestinal distress (medium chain triglyceride oil)
Dehydration/acidosis
Change in lipid profiles
Kidney stones
Growth retardation
Skeletal fractures
Rare
Pancreatitis
Cardiomyopathy
Prolonged QT syndrome
Basal ganglia injury
Vitamin and/or mineral deficiencies

New Uses for the Ketogenic Diet

Knowing that the KD can control seizures by altering the function of the central nervous system, researchers have begun to investigate the effects of the diet in other neurologic processes. Data evaluating changes in behavior and level of alertness indicate the KD has beneficial effects [59•]. The KD has even been demonstrated to improve the level of daytime sleepiness reported by patients with narcolepsy [60]. Other researchers point to shared pathophysiology between depression and epilepsy, proposing that the KD could be used as a mood stabilizer for patients with bipolar disease, noting that several anticonvulsants are already used for this purpose [61]. There has also been thought given to the potential effectiveness of the diet in children with autism [62]. Evidence also exists for the use of the KD in rats with Alzheimer's disease, as well as both humans and rats with brain tumors [63].

Conclusions

The ketogenic diet is an example of extreme dietary alteration that has proven beneficial in the treatment of epilepsy. Despite initial observations of this relationship in ancient Greece, the mechanism of why this is so continues to be a debated and studied topic in the 21st century. Most likely, the ketogenic diet has multiple and broad-acting mechanisms that may be of different importance for individual patients, seizure type, or syndrome. Clinician-scientists must continue to ask who the best candidates are for the KD, at what point it should be considered a treatment option, and continue to explore the efficacy of alternative, less restrictive dietary interventions.

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Papers of particular interest, published recently, have been highlighted as:

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- •• Of major importance

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This retrospective study found that 23 infants with predominantly intractable infantile spasms responded well to the KD, with approximately half of patients having 90% spasm reduction, electroencephalogram improvement, and developmental progression. Infantile spasm is one of the more common conditions for which many centers are using the ketogenic diet.

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One of several meta-analyses of the KD to be performed in the past decade, this review found that there were no randomized controlled trials of the KD on which to base strong favorable recommendations. However, the authors felt "a small number of observational studies lend some support for a beneficial effect."

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