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The Ketogenic Diet: Uses in Epilepsy and Other Neurologic Illnesses

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Introduction

The ketogenic diet initially was developed in the 1920s in response to the observation that fasting had antiseizure properties [1]. During fasting, the body metabolizes fat stores via lipolysis and then the fatty acids undergo beta-oxidation into acetoacetate, β-hydroxybutyrate, and acetone—ketone bodies the cell can then use as precursors to generate adenosine triphosphate (ATP). The ketogenic diet, which is very high in fat and low in carbohydrates, is thought to simulate the metabolic effects of starvation by forcing the body to use primarily fat as a fuel source. The ketogenic diet fell out of favor with the development of new anticonvulsant agents, starting with phenytoin in 1938, but it has experienced a resurgence in use over the past 20 years, particularly in the treatment of refractory epilepsy.

Ketone bodies, especially β-hydroxybutyrate, can be measured easily, so much work has centered on determining how these molecules may have anticonvulsant effects. Inconsistencies in studies attempting to correlate seizure protection with levels of ketone bodies suggest that another mechanism may be involved in the diet's beneficial effects on seizures [2–5, Class III]. Several mechanisms have been proposed, including changes in ATP production making neurons more resilient in the face of metabolic demands during seizures; altered brain pH affecting neuronal excitability; direct inhibitory effects of ketone bodies or fatty acids on ion channels; and shifts in amino acid metabolism to favor the synthesis of the inhibitory neurotransmitter GABA [6,7].

With renewed use of the ketogenic diet has come heightened interest in its potential use for other conditions (Table 1). Over the past few years, there has been an explosion in speculation about the diet's potential applications in a variety of metabolic, oncologic, neurodegenerative, and psychiatric disorders. This review examines data supporting the potential use of the ketogenic diet in each disorder and considers potential mechanisms of action in each disorder, using these data to shed light on the diet's disease-modifying effects. Both the human and animal studies discussed used standard ketogenic diets unless otherwise specified.

The ketogenic diet has many potential effects and is likely to have different mechanisms in different diseases [8]. In metabolic conditions, cancer, trauma, and ischemia, the ketogenic diet may confer a protective effect by providing an additional energy substrate to tissue at risk of cell death. However, ketosis may have more complicated effects. In one model, rats fed the ketogenic diet show marked upregulation of both the ketone transporter and the glucose transporter type 1 (GLUT-1), promoting the influx of nutrients into the brain [9]. These authors provided evidence that the ketogenic diet increases capillary density without increasing overall

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blood flow, providing a way that the diet may help nourish tissue at risk. This finding is particularly interesting in light of findings in animals with tumors, in which the diet is associated with an anti-angiogenic effect [10,11]. These discordant results eventually will need to be reconciled; they may be due to differences in angiogenic stimuli in normal cells versus malignant cells.

It is possible to discuss two aspects of the diet: known or "direct" properties (high ketone-body levels, high fat, and restriction of calories from carbohydrate) and potential indirect effects (eg, effects on neurotransmitters, ion channels, or mitochondrial biogenesis) (Table 2). Ketone bodies provide alternative substrates for use in the tricarboxylic acid cycle and enhance mitochondrial function (evidenced by increased ATP production and decreased effects of reactive oxygen species). Fatty acids and calorie restriction may have beneficial effects by themselves. The potential indirect effects have been studied in epilepsy but have not been investigated to the same degree in other illnesses. Formal studies of the efficacy of the ketogenic diet in epilepsy should serve as a model for future clinical investigations in other diseases [12••].

Treatment

Epilepsy: expanding uses

- The ketogenic diet traditionally has been used in cases of intractable epilepsy, but it also has become established as a first-line agent in a few specific epilepsy syndromes.
- Children with epilepsy due to mutations in GLUT-1, which transports glucose across the blood-brain barrier, suffer from seizures in infancy. If not identified and treated, they develop microcephaly, mental retardation, spasticity, and ataxia as a consequence of relative brain hypoglycemia. These children respond well to the ketogenic diet, as it is believed to provide an alternative fuel source for their central nervous system [13, Class III].
- Similarly, children with pyruvate dehydrogenase (PDH) deficiency show improvements while on the ketogenic diet [14, Class III]. PDH deficiency affects the cell's ability to convert pyruvate to acetyl-CoA, thereby affecting the flow of precursors from glycolysis into the tricarboxylic acid cycle and limiting mitochondrial energy production.
- Infantile spasms respond well to the ketogenic diet [15, Class II].
- Another epilepsy syndrome in which the diet may be particularly useful is Dravet syndrome (also known as severe myoclonic epilepsy of infancy). This syndrome is classically described as a prolonged febrile seizure in the first 2 years of life, followed by focal-onset seizures, myoclonus, and developmental delays [16, Class III]. Dravet syndrome is associated in many cases with mutations in the gene *SCN1A*, a subunit of the sodium channel [17].
- The ketogenic diet is also useful in myoclonic-astatic epilepsy (Doose syndrome), which is characterized by episodes of falling sometimes preceded immediately by myoclonic jerks. Other types of generalized seizures and developmental delays occur in some of these patients [18, Class III].
- The data for Dravet syndrome and myoclonic-astatic epilepsy are based on case series. Use of the diet early in the disease course is promising, but more formal trials would be beneficial, preferably with multicenter experience, given the small number of patients seen with each disorder at most centers.

- A number of patients previously refractory to multiple anticonvulsant medications become seizure-free or maintain a significant reduction in seizure frequency even after the ketogenic diet has been discontinued, suggesting the diet may have disease-modifying effects in some people with epilepsy [19,20•, Class III]. No clinical factors have been identified that predict which patients will benefit most in this regard.

Metabolic defects

- The utility of the ketogenic diet in PDH deficiency and GLUT-1 deficiency likely derives from its ability to provide 2-carbon substrates, with subsequent relief of blocks in metabolism upstream from the tricarboxylic acid cycle.
- Other genetic disorders caused by mutations limit the availability of energy substrates but do not necessarily cause seizures. One such disease is phosphofructokinase (PFK) deficiency. PFK is the rate-limiting enzyme in glycolysis for the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate. Patients with mutations in the muscle isoform of PFK demonstrate exercise intolerance with myalgias and stiffness. There also are rare infantile forms, such as a case reported by Swoboda et al. [21, Class III], with myopathy and arthrogryposis. This patient displayed marked gains in muscle strength and improvement in his developmental milestones after being placed on the ketogenic diet.
- The ketogenic diet also has been used in glycogenosis type V (McArdle disease), which is caused by a defect in the muscle-specific isozyme of glycogen phosphorylase. Glycogen phosphorylase is necessary to break down glycogen into free glucose for use as an energy source in muscles. When the ketogenic diet was applied to a patient with this disorder (presumably providing an alternative means of energy production), the patient's exercise tolerance improved and there was a trend toward decreased baseline creatine kinase levels [22, Class III].

Malignancy

- The ketogenic diet may have a role in treating disorders of cellular proliferation, especially cancer. Just as chemotherapy selectively targets tumors based on differences in the way they divide compared with normal cells, investigators have proposed targeting tumors on the basis of differences in their metabolism. Normal tissue can adapt readily to using ketones (instead of glucose) as a substrate, but malignant cells probably do not have the same degree of metabolic flexibility [23]. One case report in 1995 [24, Class III] described the use of the ketogenic diet in two girls with advanced astrocytomas, based on the idea that brain tumors are less able than healthy brain tissue to use ketones as an energy source. In this report, PET studies demonstrated a 20% reduction in glucose uptake by the tumors following the initiation of the ketogenic diet. One of the patients actually showed improvement during the course of the study and has continued to be well, without evidence of tumor progression (T. Seyfried, personal communication, 2008).
- Ketogenic diets (some using calorie restriction) have been associated with decreased tumor growth in animal models of gliomas [10], prostate cancer [25], and gastric cancer [11]. In the context of cancer, ketone bodies may provide an alternative substrate for ATP production in malignant cells, as outlined above. However, other work suggests that glucose is used to produce components critical to proliferative cell growth [26], and it is conceivable that the ketogenic diet may restrict that aspect of malignant cell transformation.

Trauma and ischemia

- Animal data suggest a role for the ketogenic diet in protection against trauma and ischemia, as ketones may be a preferred fuel in the injured brain [27]. Prins et al. [27] studied the role of the ketogenic diet in a controlled cortical impact model in rats. Young rats of varying postnatal ages underwent a small craniotomy and then, with the dura intact, were subjected to a standardized piston cylinder injury. Immediately after the impact, the rats started a standard diet or the ketogenic diet. After 1 week, a postmortem measurement of cortical contusion area was performed. The contusion area was significantly decreased in postnatal day-35 and day-45 rats that had been fed the ketogenic diet, but not in younger or older rats.
- In one hypoxia-ischemia model, rats fed a ketogenic diet for 25 days before cardiac arrest had fewer postarrest seizures and myoclonic jerks and less neurodegeneration (determined by Fluoro-Jade staining) than those fed a normal diet [28,29]. The ketogenic diet also appears to have cardioprotective properties in an isolated heart perfusion model designed to mimic global ischemia. These changes were concomitant with increased numbers of mitochondria in cardiac muscle, suggesting that improved capacity to generate energy conferred a protective effect in the face of an ischemic insult [30].

Neurodegenerative disorders

- The ketogenic diet appears to enhance mitochondrial function via a number of potential pathways. Given the important role of mitochondrial dysfunction in many neurodegenerative diseases, it is important to outline potential mechanisms of apparent disease-modifying effects of the ketogenic diet. It is unclear whether there is something specific or direct about the ketogenic diet (ie, provision of ketone bodies or fatty acids) or, perhaps more importantly, the metabolic changes it induces.
- In the case of Parkinson's disease (PD) and Alzheimer disease (AD) models, there are data suggesting that calorie restriction itself is protective [31,32••], raising the question of whether manipulations of some critical metabolic pathways also may possess disease-modifying properties. The ketogenic diet originally was designed to mimic fasting, and thus it may regulate a family of proteins known as sirtuins, which play a major role in mediating "anti-aging" effects of calorie restriction [33•]. Alternatively, the ketogenic diet may regulate a master energy-sensing protein in the cell, 5′-adenosine monophosphate (AMP)–activated kinase [34]. Both proteins have a number of downstream effectors that may possess neuroprotective properties.
- Finally, with its low carbohydrate content, the ketogenic diet's impact on glucose use and factors such as brain-derived neurotrophic factor (one example of a potential indirect effect of the diet) may be important [35,36].

Parkinson's disease

- PD is a neurodegenerative condition in which the impairment of mitochondrial complex I activity is hypothesized to play a role in the death of the dopaminergic neurons of the substantia nigra pars compacta. Various investigators have hypothesized that ketones could bypass complex I to provide an alternative fuel source for neurons at risk. Alternatively, ketone bodies may enhance mitochondrial function and thus ATP production, thereby protecting cells against various insults that demand high levels of usable energy.
- In a model of PD, neurons cultured from the developing mesencephalon, the site of the future substantia nigra, are susceptible to injury and death from the application of

1-methyl-4-phenylpyridinium (MPP^+), which inhibits mitochondrial energy production. Adding one of the ketone bodies, β-hydroxybutyrate, rescues these cells from death and reduction in neurite outgrowth [37]. In an in vivo model, mice treated with β-hydroxybutyrate via continuous subcutaneous infusion were relatively protected from the dopaminergic degeneration induced by injection of MPTP, an MPP^+ precursor, apparently by enhancing oxidative phosphorylation and the production of ATP [38].

- With this rationale, VanItallie et al. [39, Class III] performed a feasibility study with PD patients and the ketogenic diet. They explored whether PD patients would be able to prepare the ketogenic diet in their homes and remain on it for at least 1 month. Of seven patients enrolled, five completed the study. They were monitored for ketone levels and weekly Unified Parkinson Disease Rating Scale (UPDRS) scores. All the patients lost weight. Interestingly, the mean decrease in UPDRS scores was 43.4%. A placebo effect is not ruled out, but this result at least suggests that the ketogenic diet was not harmful and certainly invites further study into its role in preserving neuron function in PD and other neurodegenerative diseases. The possibility that the diet may have altered levodopa absorption (and that this factor, rather than an effect of the diet on neuronal function, was responsible for the change) has not been studied rigorously [40].

Alzheimer disease

- The ketogenic diet also may function in a neuroprotective fashion in AD. In this progressive dementia, extracellular plaques containing amyloid protein are thought to be central to the pathogenesis of the disease. β-Hydroxybutyrate protects against the toxicity directly induced by the addition of fragments of amyloid-β (Aβ)1-42 in cultured hippocampal neurons [37]. The ketogenic diet also may protect against the deposition of amyloid. One theory of how the ketogenic diet may affect AD is that ketone bodies allow the cell to overcome amyloid-induced PDH dysfunction [37].
- The ketogenic diet also may protect against the deposition of amyloid. Van der Auwera et al. [41] studied the ketogenic diet's effects on AD using a transgenic mouse model of AD in which mice express a mutated human amyloid precursor protein gene in postmitotic neurons. These mice develop significant soluble Aβ by 3 months of age, and then brain plaques by 12 to 14 months. They also demonstrate behavioral deficits in tests of object recognition. In their study, 16 mice were fed a regular diet until 3 months of age, at which point 8 mice were switched to the ketogenic diet, without restriction on intake. After about 40 days on the diet, the animals fed the ketogenic diet had 25% less soluble Aβ in their brains. However, they did not perform any differently on tests of cognitive function than the mice fed a standard diet. The prevailing paradigm that reductions in Aβ deposition may delay progression in AD makes these findings particularly intriguing; perhaps a longer period on the ketogenic diet would reveal some behavioral differences between the two groups of mice.
- In AD, ingestion of carbohydrates may worsen memory [42]. Patients with cognitive impairment lacking the APO-ε4 allele (one of the risk factors for AD) showed improved scores on the Alzheimer Disease Assessment Scale–Cognitive Subscale after ingesting a medium-chain triglyceride shake, which induces low but measurable levels of ketosis [43, Class I]. Scores on this test for those with the APO-ε4 allele (as well as scores for all patients on some other tests administered in this study) were not improved after ingestion of the medium-chain triglyceride shake, making the generalizability of these findings to other patients with cognitive impairment (including AD) an area for further investigation.

- One potential confounder of ketogenic diet studies is another direct effect of the diet—increased levels of fatty acids. Dietary supplementation of essential fatty acids can improve cognitive dysfunction, including in patients with AD [44, Class II]. This suggests that something other than ketone bodies (in this case, essential fatty acids) may have beneficial effects in neurodegenerative diseases. Essential fatty acids may have a beneficial effect on learning in rodent models, raising the possibility that they may have neuromodulatory properties of their own [45,46].

Amyotrophic lateral sclerosis

- Recent animal studies suggest a role for the ketogenic diet as a potential therapy for amyotrophic lateral sclerosis (ALS). ALS results from the death of motor neurons in the brain and spinal cord. A small number of cases are caused by an inherited mutation in the gene encoding the Cu/Zn superoxide dismutase I (SOD1). Mice expressing the mutated gene recapitulate the progressive muscle weakness and death due to respiratory failure seen in humans with ALS. Various lines of evidence suggest that mitochondrial dysfunction may play a role in the pathogenesis of ALS. A recent study suggests that ketosis induced by the ketogenic diet might affect progression of the disease [47]. Transgenic SOD1 mice fed a high-fat diet (60% of calories from fat, compared with < 10% fat in standard rodent chow and > 90% of calories from fat in a typical rodent ketogenic diet) preserved their performance on a standard rotorod test longer than those fed a regular diet. Mice were fed ad lib, and mice fed the high-fat diet gained more weight than those on the standard diet, so overall caloric restriction was unlikely to be a factor in this study. When spinal cords were examined, significantly more motor neurons were preserved in the mice fed the ketogenic diet than in those fed a regular diet. However, the ketogenic diet did not significantly prolong survival.
- When mitochondria were isolated from these SOD1 mice, β-hydroxybutyrate rescued ATP production in the presence of a complex I inhibitor. It also helped to preserve neurons in culture exposed to the same inhibitor, paralleling the findings found for PD. In these neurodegenerative disorders, the ketogenic diet may be providing substrate to bypass impaired or poorly functioning complex I. Another hypothesis on enhanced ATP production includes increased mitochondrial biogenesis [48•]. Alternatively, decreased reactive oxygen species generation (which protects the process of oxidative phosphorylation) could be the result of an effect on NADH oxidation or preventing adverse events in the handling of calcium overload in mitochondria, such as the mitochondrial permeability transition [48•,49,50].

Other disorders

- Ketogenic diets have been studied in patients with other neurologic and psychiatric disorders, even though its mechanism of action for these disorders is unclear.

Autism

- In one study, a variant of the ketogenic diet was applied to children with autism [51, Class III]. This diet was a modified John Radcliffe diet, which substitutes medium-chain triglycerides for some fat, but it was administered for only 4 of every 6 weeks during this 6-month trial (ie, cycles of 4 weeks “on diet” and 2 weeks “off diet” were used for the duration of the study). This group studied children on Crete, an island with a relatively isolated population and a significant number of autistic children. Behavior was rated on the standardized Childhood Autism Rating Scale (CARS) by a blinded child psychiatrist. Of the 18 children who completed the study, 2 demonstrated significant improvement (ie, CARS score reduced by > 12 points), 8

had moderate improvement (CARS score reduced by 8–12 points), and 8 showed minor improvement (CARS score reduced by 2–8 points). Children with lower starting CARS scores (less severe autism) appeared to respond better than those more severely affected. These findings should be interpreted with caution for a number of reasons. Given the geographic isolation of Crete, there may have been a strong genetic contribution to autism in this population. Methodologically, the CARS score was not designed as a longitudinal test, making its meaning in this study unclear. Additionally, intermittent administration of the ketogenic diet has not been examined in other disorders, making it difficult to compare this intervention with other studies of the ketogenic diet. Finally, any structured intervention may be associated with improved performance in patients with autism. Further study with appropriate controls (structured diet plans, vitamin administration) is needed to confirm these findings.

Depression

- The ketogenic diet has been studied in an animal model of depression. Murphy et al. [52] used a testing paradigm called the Porsolt test (a forced choice model) to study the ketogenic diet. Their findings suggest that the ketogenic diet can result in behavioral changes similar to those seen after antidepressants are administered.

Migraine headache, narcolepsy

- Dietary therapies similar to the ketogenic diet also may be useful in the treatment of migraine headaches and narcolepsy, and as we learn more about the mechanisms of action of the ketogenic diet, other potential applications undoubtedly will be suggested.
- In 2006, Strahlman [53, Class III] reported the case of his own wife, whose intractable migraine headaches resolved after a medically supervised low-calorie diet. Husain and colleagues [54, Class III] studied an Atkins diet–like plan in patients with narcolepsy and reported an 18% decrease in daytime sleepiness as measured by a standard questionnaire. The Atkins diet is less restrictive than the ketogenic diet and does not contain as much fat as “classic” ketogenic diets.

Opinion statement

The ketogenic diet is well established as therapy for intractable epilepsy. It should be considered first-line therapy in glucose transporter type 1 and pyruvate dehydrogenase deficiency. It should be considered early in the treatment of Dravet syndrome and myoclonic-astatic epilepsy (Doose syndrome).

Initial studies indicate that the ketogenic diet appears effective in other metabolic conditions, including phosphofructokinase deficiency and glycogenosis type V (McArdle disease). It appears to function in these disorders by providing an alternative fuel source. A growing body of literature suggests the ketogenic diet may be beneficial in certain neurodegenerative diseases, including Alzheimer disease, Parkinson’s disease, and amyotrophic lateral sclerosis. In these disorders, the ketogenic diet appears to be neuroprotective, promoting enhanced mitochondrial function and rescuing adenosine triphosphate production.

Dietary therapy is a promising intervention for cancer, given that it may target the relative inefficiency of tumors in using ketone bodies as an alternative fuel source. The ketogenic diet also may have a role in improving outcomes in trauma and hypoxic injuries.

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Table 1

Potential uses of ketogenic diet in various illnesses (clinical and laboratory studies)

Disorder	Highest clinical class of evidence	Potential mechanisms of action
Neurologic		
Epilepsy	I	Enhanced mitochondrial function, fatty acid effect on ion channels, neurotransmission and neurotransmitters, decreased effects from reactive oxygen species
Alzheimer disease/cognitive impairment	I	Decreased beta amyloid deposition, relief of block in PDH
Parkinson's disease	III	Enhanced mitochondrial function
Amyotrophic lateral sclerosis		Enhanced mitochondrial function
Traumatic brain injury		Substrate delivery, enhanced mitochondrial function
Hypoxic/ischemic brain injury		Substrate delivery, enhanced mitochondrial function
Autism	III	Enhanced mitochondrial function
Depression	III	Enhanced mitochondrial function
Headaches	III	Enhanced mitochondrial function
Narcolepsy	III	Enhanced mitochondrial function
Metabolic		
GLUT-1 deficiency	III	Substrate delivery
PDH deficiency	III	Substrate delivery
PFK deficiency	III	Substrate delivery
Glycogenosis type V (McArdle disease)	III	Substrate delivery
Other		
Cancer (astrocytomas, prostate, gastric)	III	Substrate delivery
Cardiac ischemia		Substrate delivery, enhanced mitochondrial function

GLUT-1—glucose transporter type 1; PDH—pyruvate dehydrogenase; PFK—phosphofructokinase.

Table 2

Potential mediators of the effect of the ketogenic diet in neurologic disorders

Direct
Ketone bodies
Substrate delivery
Enhancement of mitochondrial function
Adenosine triphosphate production
Decreased effects from reactive oxygen species
Fatty acids
Calorie restriction
Indirect
Neurotransmission
Neurotransmitters
Neuropeptides
Ion channels
Mitochondrial biogenesis