

# The Ketogenic Diet

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**Background:** The ketogenic diet is a low-carbohydrate, adequate-protein, and high-fat diet with a long history of use for the treatment of intractable seizures in children. This dietary therapy has been enjoying increasing popularity in recent years, despite the availability of increasing numbers of new antiepileptic drugs and surgical treatments.

**Review Summary:** The authors review the history of the ketogenic diet, the traditional protocol in initiating it, possible mechanisms of its action, evidence for efficacy, and side effects. In addition, they highlight some of the areas of active research in this field as well as future directions and unanswered questions.

**Conclusion:** The ketogenic diet is an efficacious and relatively safe treatment of intractable seizures. Despite its long history, however, much remains unknown about the diet, including its mechanisms of action, the optimal protocol, and the full range of its applicability. Investigations of the diet are providing new insight into the mechanisms behind seizures and epilepsy itself, as well as possible new therapies.

**Key Words:** epilepsy, intractable seizures, ketogenic diet, dietary therapy

(*The Neurologist* 2005;11: 161–170)

There have been anecdotal reports of the efficacy of dietary therapy, especially starvation, for the treatment of epilepsy since Biblical times. In fact, early treatments for epilepsy relied heavily on strict dietary regimens.<sup>1</sup> More scientific reports began to appear in the early part of the 20th century. In 1911, Guelpa and Marie<sup>2</sup> reported the use of fasting as an epilepsy treatment in France. This led to the publication of several case reports and small case series demonstrating the efficacy of fasting for seizure control.<sup>3–5</sup> In 1921, R. M. Wilder<sup>6</sup> at the Mayo Clinic proposed in 1921 an actual diet that would mimic the biochemical changes that occur during fasting (ie, acidosis, dehydration, and ketosis). This ketogenic diet worked by providing a regimen of 1g/kg protein, 10 to 15 g/day carbohydrate, and the remaining

calories as fat.<sup>7</sup> This is quite similar to the classic ketogenic diet in use nearly a century later.

Over the next 20 years, there was widespread popularity of the ketogenic diet for treatment of seizures in children and even some adults.<sup>8</sup> However, after the introduction of diphenylhydantoin in 1938, followed by other anticonvulsants, the popularity of the ketogenic diet waned. For several decades, the ketogenic diet was used only at several academic centers, and research into the diet was minimal. Clinical and research interest in the ketogenic diet was renewed in the early 1990s after a 2-year-old boy with intractable seizures was treated with the ketogenic diet at the Johns Hopkins Hospital.<sup>9</sup> He responded extremely well, leading his father to create the Charlie Foundation, which has helped to inform both patients and physicians about the ketogenic diet ([www.charliefoundation.org](http://www.charliefoundation.org)). In the intervening decade, more than 200 clinical and research studies have been published about the ketogenic diet. The diet is now well established in the medical community and is even reimbursed by insurance companies, including Blue Cross and Blue Shield.<sup>10</sup> In this review we discuss both the clinical and basic science aspects of the ketogenic diet, including how it is currently applied, the possible mechanisms behind its efficacy, and future directions in both the clinical utility of the diet and of our understanding of how it works.

*Implementation of the ketogenic diet requires a team approach—including physicians, nurses, and especially nutritionists who have been specifically trained in the management of patients on this diet.*

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ISSN: 1074-7931/05/1103-0161

DOI: 10.1097/01.nrl.0000160818.58821.d2

## CURRENT PROTOCOL

Implementation of the ketogenic diet requires a team approach—including physicians, nurses, and especially nutritionists who have been specifically trained in the manage-

ment of patients on this diet. It is also helpful to include pharmacists knowledgeable about the carbohydrate content of medications. The availability of nutritionally labeled products is also crucial, which has led to occasional difficulty internationally.

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*The main indication for the ketogenic diet is the presence of seizures that are difficult to control.*

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### Patient Selection

The main indication for the ketogenic diet is the presence of seizures that are difficult to control. Traditionally, it has been used for patients with generalized seizures who have responded poorly to medications, especially those with multiple seizure types, such as those that occur in Lennox-Gastaut syndrome. However, the efficacy of the diet appears to be independent of seizure type.<sup>11,12</sup> In addition, patients who have adequate control but intolerable side effects from medication may be considered for the ketogenic diet.<sup>13</sup>

The ketogenic diet is indicated as first-line therapy for children with glucose transporter deficiency (GLUT-1) or pyruvate dehydrogenase deficiency.<sup>14-16</sup> For both conditions, the utilization of sources of energy other than glucose for brain metabolism can prevent seizures by providing acetyl-CoA directly into the tricarboxylic acid (TCA) cycle without prior glycolysis. In these situations, the diet is not only helpful but also life-saving.

Because the ketogenic diet is associated with major shifts in cerebral energy metabolism, some authors caution against using the diet in patients with certain metabolic disorders. These include pyruvate carboxylase deficiency, mitochondrial disorders, and fatty acid oxidation problems.<sup>17</sup> Nevertheless, we have successfully treated several patients with mitochondrial disorders with the ketogenic diet with carnitine supplementation and careful monitoring.

### Initiation

The actual dietary components are individually calculated for each patient, incorporating both daily calories, fluids, and the ratio of fat to protein and carbohydrates, ranging from 2:1 to 4:1, with higher ratios more restrictive. Several factors are considered in these calculations, including age, height, weight, and activity level. Young children and infants as well as adolescents are typically started on a 3:1 ratio to be able to provide extra protein and to allow adolescents increased choices of foods. Most other children are started on a 4:1 ratio. The protein component is based on the

protein requirements for age and size; carbohydrates are typically 5 to 10 g/day, with the remainder of calories as fat. Total calories are typically targeted at about 75% of recommendations for age, although allowances are made for the starting weight of the child. For an infant on formula or a patient who is tube fed, a liquid ketogenic diet composed of fats including Microlipid (Mead Johnson Nutritionals, Evansville, Indiana), protein (Ross Carbohydrate-free; Abbott Laboratories, Abbott Park, Illinois), carbohydrate (Polycose, Abbott Laboratories), and water is prepared. This is perhaps the easiest method of providing the diet.<sup>18</sup> A powdered, 4:1-ratio formula has been created (KetoCal™; SHS International, Rockville, Maryland). Older children are given computer-generated menus that offer 3 daily meals and a snack. Fluids are usually also restricted to 80% of daily needs. If there is a history of renal calculi or the patient is concurrently on a carbonic anhydrase inhibitor (eg, topiramate, acetazolamide, or zonisamide), fluids are increased to 100%. Although fluids and calories are traditionally restricted to improve ketosis, there is little evidence regarding the necessity of this.

The specific protocol used at the Johns Hopkins Hospital is described in Table 1. Children are admitted to the hospital for a 5-day period during which the ketogenic diet is gradually advanced after a 24- to 48-hour fast. There are some data to suggest that the initial period of fasting is not necessary for long-term ketosis and that the diet can be initiated at home without hospitalization.<sup>19</sup> However, the initial fast occasionally provides immediate improvement in seizure control, which can be encouraging to the patient and family.<sup>20</sup> In addition, the hospitalization is a valuable opportunity to watch for any acute worsening on the diet, as might be seen in an unrecognized metabolic disorder, and to provide adequate education for the families. Long-lasting friendships that develop between families during the admission week are not unusual. Acute problems periodically seen during fasting include hypoglycemia, vomiting, dehydration, and food refusal. The patient's medications are also reviewed and adjusted during the admission to make sure that they are free of carbohydrates as many, especially liquids, have high carbohydrate content that can interfere with ketosis.<sup>21</sup>

Another version of the ketogenic diet, based on medium-chain triglyceride (MCT) oil, was developed in the late 1960s.<sup>22</sup> The motivation for development of this diet was that MCT oils are more strongly ketogenic than longer fatty acids. This reduces the amount of fat that is required in the diet, allowing a larger amount of protein and even carbohydrates. This version of diet, however, can cause gastrointestinal distress in patients (stomach cramps and diarrhea) and is used now only occasionally. MCT oil is often incorporated in the classic ketogenic diet for a variety of reasons, including increasing the protein and carbohydrate allowances, countering constipation, or improving dyslipidemia.

**TABLE 1.** Johns Hopkins Hospital Protocol for Initiation of Ketogenic Diet

|   |
|---|
| Before diet   |
| Minimize carbohydrates for 1–2 d  |
| Start fasting after dinner on evening before admission  |
| Day 1   |
| Admit to hospital   |
| Continue fasting  |
| Use carbohydrate-free medications   |
| Restrict fluids (without caffeine or carbohydrates) to 60–75 mL/kg (maximum, 1200 mL)             |
| Dextrostix every 6 hr; if glucose <40 mg/dL, then every 2 hr                                      |
| If patient is symptomatic or glucose <25 mg/dL, give 30 mL orange juice and measure again         |
| Day 2   |
| Continue fasting  |
| Dinner: one third of calculated ketogenic diet meal as “eggnog”                                   |
| Excessive ketosis (nausea or vomiting) relieved with small amounts of orange juice                |
| Day 3   |
| Breakfast and lunch: one third of calculated meal as “eggnog”                                     |
| Dinner: two thirds of calculated meal as “eggnog”   |
| Day 4   |
| Breakfast and lunch: two thirds of calculated meal as “eggnog”                                    |
| Dinner: first full ketogenic meal   |
| Severe ketosis/acidosis managed with additional carbohydrate-free fluids                          |
| Day 5   |
| Breakfast: full ketogenic meal  |
| Discharge with prescription for sugar-free, fat-soluble vitamin supplement and additional calcium |

**Maintenance**

Patients are discharged home with prescriptions for daily multivitamin and calcium supplements. After discharge, urine ketones are checked several times per week by parents, and the diet is adjusted to maximize seizure control (via telephone or e-mail contact). Weight is monitored periodically. Laboratory values (urine calcium and creatinine, urinalysis, fasting lipid profile, electrolytes, and a complete blood count) are checked every 3 to 6 months. Adjustments to calorie content and the ratio are made as needed on an individual basis to maximize ketosis and to minimize hunger and undesired weight changes. Anticonvulsant medications are typically not changed immediately after starting the diet; later they are adjusted, often downward, on a case-by-case basis. If medication side effects are significant, they can be tapered and discontinued even as early as the diet admission.<sup>23</sup>

Periods of increased seizure activity while the patient is on the ketogenic diet require careful management. Specifi-

cally, it is important to ensure that the patient is not accidentally receiving additional carbohydrates from some unknown source. Common culprits are new medications or food additives that are labeled as “sugar free” but may still contain large amounts of carbohydrates such as maltodextrin, sorbitol, starch, or fructose. Next, urine ketones are checked to assess ketosis. If ketones are not 4+ or more than 160 mg/dL, then a 24-hour fast with clear liquids can be used to improve ketosis rapidly. Lastly, antiepileptic medications can be adjusted or periodic benzodiazepines can be used. Similar to the effect on all children with epilepsy, illness or stress can lead to breakthrough seizures; it is important to avoid the temptation to make dietary changes in these situations.

**Side Effects**

Any beliefs that the diet is “holistic” or “all-natural” are erroneous.<sup>24</sup> The diet is not without side effects, which can be grouped into common, less common, and rare (case reports; Table 2). Gastrointestinal complaints from the classic diet include constipation and worsening of reflux, and from the MCT version, diarrhea and abdominal cramps. These complaints can usually be treated effectively with minor adjustments to the diet, stool softeners, laxatives (Miralax™; Braintree Laboratories, Braintree, Massachusetts), and fluids. Acidosis is a major concern during both diet initiation and acute intercurrent illnesses. It is important that the patient and family understand signs of acidosis and how to hydrate with carbohydrate-free fluids. Most children on the diet have a low baseline acidosis, with HCO<sub>3</sub><sup>-</sup> of 12 to 18 mg/dL. The issue of whether carnitine supplementation should be used (or acylcarnitine levels checked) is still controversial. We tend to

**TABLE 2.** Side Effects of the Ketogenic Diet

|                                   |
|-----------------------------------|
| Common                            |
| Acidosis                          |
| Nausea/vomiting during initiation |
| Weight loss                       |
| Constipation (classic diet)       |
| Diarrhea (MCT version)            |
| Less common                       |
| Hyperlipidemia                    |
| Worsening of GERD (classic diet)  |
| Renal calculi                     |
| Inadequate or slowed growth       |
| Rare (case reports)               |
| Prolonged QT intervals            |
| Bruising                          |
| Selenium and vitamin deficiency   |
| Basal ganglia change              |
| Pancreatitis                      |
| Fanconi renal tubular acidosis    |

supplement carnitine if the patient complains of otherwise unexplained fatigue after the diet is started and calories have already been optimized.

Growth difficulties also can occur with the ketogenic diet. In a prospective study of 237 patients, there was an initial drop in percentiles for both the weight-for-age and height-for-age categories.<sup>25</sup> While patients still grow at rates within the normal range, it is clear that growth is decreased with the diet and that younger children are at the highest risk. A smaller (25 patients) and shorter (4 months) prospective study of the classic diet found that patient's heights grew appropriately but they had significant decreases in their weights.<sup>26</sup> Therefore, a considerable portion of the ongoing management of children on the ketogenic diet is devoted to monitoring their growth and nutritional status and making adjustments to the diet as needed.

The incidence of renal calculi in children on the ketogenic diet is 5 to 6%.<sup>27,28</sup> The diet can cause hypercalciuria, urine acidification, and hypocitraturia, increasing the risk of uric acid and, less commonly, calcium phosphate and oxalate stones. Because of this risk, there has been concern about using the diet in children on carbonic anhydrase inhibitors, such as acetazolamide, topiramate, and zonisamide, which also increase the risk of nephrolithiasis. Nevertheless, in a retrospective analysis, there appeared to be no increased risk associated with combined use of carbonic anhydrase inhibitors and the diet compared with the diet alone.<sup>28</sup> Based on this study, it is recommended that patients being treated with these medications should initially receive increased hydration and oral polycitrates (Polycitra K™, 2 mEq/kg/day divided twice daily) if there is a family or personal history of kidney stones. If a patient does develop renal stones, the first step is to discontinue any concomitant carbonic anhydrase inhibitors. Although its clinical utility has not been evaluated, urine alkalinization with oral polycitrates is also recommended for patients with hematuria or urine calcium-to-creatinine ratios more than 0.2.

Another known side effect is hyperlipidemia.<sup>29-31</sup> A prospective study of children on the classic diet showed significant elevations of total cholesterol, triglycerides, and the atherogenic apolipoprotein B containing lipoproteins (LDL and VLDL). There was a significant reduction of the antiatherogenic apolipoprotein A-containing lipoproteins (HDL).<sup>31</sup> Whether these changes actually lead to atherogenesis is not known and requires further investigation. The MCT diet may produce less dyslipidemia,<sup>22,32</sup> and incorporating MCT oil into the diet is an option for patients in whom dyslipidemia is a major concern.

A recent study in rats suggested that the diet led to impaired brain growth and severe impairment in visual-spatial memory.<sup>33</sup> In humans, this has not been seen, and one study revealed improved cognitive functioning.<sup>34</sup> Behavior may also be improved, but it is difficult to know how much

of this improvement is attributable to improved seizure control.<sup>35</sup> In adults fed a ketogenic diet for weight reduction, impairments in higher order mental processing and flexibility have been reported.<sup>36</sup> This will be important to resolve, especially if the diet is to be applied in situations when other therapeutic options are available or the seizures are not severely debilitating to the patient.

Some side effects have been reported in small series of patients or single case reports. Their clinical significance and causal relationship with the diet have not been established. These include reports of cardiomyopathy likely related to selenium deficiency<sup>37</sup> and QT prolongation.<sup>38</sup> Acute pancreatitis has been reported in 2 patients.<sup>39,40</sup> Without proper supplementation with vitamins and minerals, deficiencies of vitamin D and calcium,<sup>41</sup> and trace minerals such as copper,<sup>42</sup> selenium,<sup>37</sup> and zinc<sup>43</sup> have been reported. Deficiencies of vitamins, especially water-soluble vitamins, and certain minerals are rare (most notably calcium and trace minerals) and are easily avoided by supplementation of these substances, which is routinely done.

### Diet Discontinuation

If the diet has led to seizure freedom for 2 years, side effects are intolerable, or the family does not feel that the diet is worth the effort, we will recommend discontinuation of the diet. This can be done in 2 ways, the first option being a lowering of the ratio to 2:1 or 2.5:1. This is then followed by increasing the portions of foods that are on the diet, and finally liberalizing carbohydrates. It can also be done more rapidly by substituting whole milk, then 2%, then 1%, and, as ketosis drops, adding carbohydrates.

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*A meta-analysis of studies from 1925 to 1998 reported that 37% of patients have more than 90% reduction in seizures and an additional 30% have a 50 to 90% reduction.*

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### EFFICACY

A meta-analysis of studies from 1925 to 1998 (including both classic ketogenic and MCT diets) reported that 37% of patients have more than 90% reduction in seizures and an additional 30% have a 50 to 90% reduction.<sup>44</sup> In the largest prospective study to date of 150 children, at 3 months, 3% were seizure-free, 31% had more than 90% reduction in seizure frequency, and an additional 26% had a 50 to 90% reduction in seizure frequency.<sup>11</sup> At 12 months, these num-

bers were 7% (seizure free), 20% (>90% reduction), and 23% (50–90% reduction). In this study, improvement in seizure control was independent of age (mean age, 5.3 years; range 1–16 years), gender, or seizure type. A multicenter prospective study also demonstrated similar results for patients with generalized or multifocal seizures (55% with >50% reduction at 6 months, and 40% at 1 year).<sup>45</sup> The efficacy of the MCT diet has only been demonstrated in small series of patients, but it appears to be similar to that of the classic ketogenic diet.<sup>22,32,46</sup> A large, multicenter study comparing the 2 diets is currently underway in England.

Whether certain disease states are more amenable to the diet or whether the diet could be beneficial first-line remains to be proved.<sup>47</sup> A small retrospective study demonstrated the efficacy of the ketogenic diet for infantile spasms and for the associated hypsarrhythmia pattern on the EEG.<sup>48</sup> When successful in reducing seizures, the diet also has benefits in terms of decreased cost of care and medications.<sup>49,50</sup>

Only limited data are available regarding the efficacy of the diet in older children and adults. Adolescents appear to derive benefit from the diet, without higher rates of noncompliance.<sup>51</sup> Barborka<sup>8</sup> reported the results for 100 patients (age, 15–51 years): At 1 year, 12% became seizure free, 44% had definite improvement, and 44% had no improvement. In the modern era, only 1 group at Jefferson Medical College has reported data on adults on the ketogenic diet, with similar results, although in a much smaller group of patients.<sup>52,53</sup> Although the diet has been found to be effective for adults, it does appear to be more effective in children.<sup>54</sup> This is also true in animal models.<sup>55,56</sup> One reason for this finding may be that younger animals appear to produce a higher degree of ketosis on the diet and that the brains of younger animals preferentially use ketone bodies as a substrate compared with adults.<sup>57</sup>

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*The efficacy of the ketogenic diet in suppressing seizures in animal models has been demonstrated by many investigators in many different models.*

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Unlike most antiepileptic medications, the efficacy of the diet for suppressing seizures in experimental animals was demonstrated long after it had been well established in humans. Animal models of the ketogenic diet were first reported in the 1970s.<sup>58,59</sup> The efficacy of the ketogenic diet in suppressing seizures in animal models has been demonstrated by many investigators in many different models,

including electroshock,<sup>58–60</sup> kindling,<sup>61</sup> and pentylenetetrazole-induced seizures.<sup>62</sup> Of note, however, not all investigators have found anticonvulsant or antiepileptic effects.<sup>63,64</sup>

Although the data overwhelmingly support the efficacy of the ketogenic diet for seizure reduction, a double-blind, placebo-controlled study has never been performed. This is largely due to the difficulty of designing a true double-blind study involving such a rigorous treatment modality.<sup>44</sup> A short-term, crossover-design study involving the rapid induction of ketosis with fasting, followed by subsequent treatment with the ketogenic diet with saccharin versus the ketogenic diet with glucose (placebo arm), has recently been completed at our institution, but the results have not been analyzed.

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*Institution of the ketogenic diet leads to major changes in the basic biochemistry and physiology of the central nervous system.*

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### MECHANISMS OF ACTION

Institution of the ketogenic diet leads to major changes in the basic biochemistry and physiology of the central nervous system. Under conditions of reduced serum glucose, ketone bodies (acetoacetate,  $\beta$ -hydroxybutyrate, and acetone) are formed in the liver from metabolism of fatty acids. Long-chain fatty acids are released from adipose tissue and are transported to the liver, where they enter the mitochondria via the carnitine acyltransferase system.<sup>65</sup> There they undergo fatty acid oxidation and are converted to acetyl-CoA, which is then converted to ketone bodies. Medium-chain fatty acids are also converted to acetyl-CoA but are able to bypass the acyltransferase system—partially explaining why MCT oils are more ketogenic than their longer counterparts.<sup>66</sup> Ketone bodies are transported into the brain via a monocarboxylic acid transporter.<sup>67</sup> In starvation states, ketone bodies are used efficiently by the body and can provide nearly 70% of the brain's energy requirements.<sup>68</sup> It has proved difficult to determine which of these many changes or their downstream effects are actually responsible for the diet's efficacy. It seems likely that more than 1 mechanism is actually responsible. The proposed mediators and mechanisms are outlined in Table 3 and are discussed below.

Without regard to the specific mediator, many authors have investigated the effects of the diet on the electrophysiologic properties of brain, usually hippocampal, tissue both in vivo and in vitro with somewhat conflicting results. The diet does not appear to alter baseline synaptic transmission, evoked responses, and excitability (as tested in Mg<sup>2+</sup>-free

**TABLE 3.** Possible Mediators for the Action of the Ketogenic Diet

|  |
|--|
| Acidosis   |
| Ketone bodies/ketosis ( $\beta$ -hydroxybutyrate, acetoacetate, acetone) |
| Dehydration  |
| Calorie restriction  |
| Polyunsaturated fatty acids  |
| Increased energy reserve   |
| Glutathione peroxidase   |
| Mitochondrial uncoupling proteins  |

medium) in hippocampal slices from rats fed a diet for 6 to 8 weeks compared with control rats.<sup>69</sup> It has been argued that the lack of difference was due to the presence of glucose in the solution used to maintain the brain slices *in vitro*.<sup>70</sup> In fact, when investigated *in vivo*, the diet did increase paired pulse inhibition in the dentate gyrus, consistent with a possible enhancement of GABA-ergic inhibition.<sup>70</sup> Of note, after kainic acid-induced status epilepticus, slices from diet-fed rats showed decreased excitability compared with slices from rats fed control diet,<sup>69</sup> suggesting that the diet caused or prevented some long-term alteration that reduced the effects of status epilepticus. This is consistent with the anecdotal observation that the beneficial effects of the diet often outlast the period that the patient is in ketosis.

Both starvation and the diet lead to serum acidosis. In 1928, Lennox<sup>71</sup> proposed that this was responsible for the anticonvulsant action. Acidosis can have multiple actions that could diminish neuronal excitability and seizure susceptibility, such as decreased sensitivity of the NMDA subtype of glutamate receptors<sup>72,73</sup> or decreased gap junction coupling.<sup>74</sup> Multiple investigators, however, have failed to document a significant change in cerebral pH with ketosis,<sup>75-77</sup> but these studies have relied on relatively crude or indirect methods of measuring intracellular pH. Localized but significant changes in pH cannot be ruled out. Davidian et al<sup>75</sup> did find a small degree of intracellular acidosis with the MCT version of the diet.

Many authors have proposed that ketone bodies and/or ketosis are the primary mediators of the efficacy of the diet. One of the earliest and more popular theories was that ketone bodies may have direct anticonvulsant actions. The ketogenic diet increases the levels of all 3 ketone bodies in the serum and the CSF. There appears to be a minimum threshold level of ketone body concentration required for seizure control.<sup>52,78</sup> Also, rapid reversal of ketosis by giving carbohydrates<sup>78,79</sup> or by acute inhibition of fatty acid oxidation by using mercaptoacetate<sup>80</sup> has been shown to reverse the anticonvulsant effects of the diet. Nonetheless, contrary to what would be expected for a direct anticonvulsant action, a direct correla-

tion between the degree of ketosis (concentration of ketone bodies) and the level of seizure control has generally not been found.<sup>59,61,80,81</sup>

One alternative explanation for this finding is that different ketone bodies may have differential effects in preventing seizures, and most of these studies only evaluated overall ketosis or  $\beta$ -hydroxybutyrate concentrations. Rho et al<sup>82</sup> found that acetoacetate and acetone reduced sensory-evoked seizures in Frings audiogenic seizure-susceptible mice, but  $\beta$ -hydroxybutyrate did not. Also, Likhodii et al<sup>83</sup> recently demonstrated that intraperitoneal injection of acetone suppresses seizures in multiple epilepsy models. Using magnetic resonance spectroscopy to measure levels of ketone bodies in the brains of 7 patients on the ketogenic diet, Seymour et al<sup>84</sup> found that, of the 3 types of ketone bodies, only acetone levels are increased in the brain of patients on the diet; however, 2 patients had seizure control without elevated brain acetone levels, suggesting that it is at least not the sole mechanism responsible for seizure control. Direct application of  $\beta$ -hydroxybutyrate or acetoacetate does not appear to alter excitatory or inhibitory transmission in hippocampal brain slices or cultured neurons.<sup>85</sup>

Some authors have postulated that the metabolism of ketone bodies in the brain leads to changes in glutamate metabolism that are responsible for the antiepileptic effects of the diet.<sup>86</sup> Specifically, it is postulated that because ketone body metabolism, which must proceed through acetyl-CoA, requires the conversion of oxaloacetate to citrate as part of the TCA cycle, less oxaloacetate is available for the transamination of glutamate to aspartate. Indeed, in astrocyte cultures, ketone bodies do reduce transamination of glutamate,<sup>87</sup> and aspartate concentrations are decreased in the brains of animals on the ketogenic diet.<sup>76</sup> The increased pool of glutamate is then available for the synthesis of both GABA and glutamine, a precursor for GABA. This has been demonstrated in synaptosomes exposed to ketone bodies.<sup>88</sup> Also, because of the increased levels of acetate in the brain during ketosis, it is postulated that direct production of glutamine via glial cells is also increased. Although limited electrophysiologic evidence suggests that inhibitory synaptic transmission, mediated by GABA<sub>A</sub> receptors, is increased in the dentate gyrus of rats on the diet,<sup>70</sup> crude measurements have failed to detect elevated levels of GABA in the brain of animals on the diet.<sup>59,77</sup> Such measurements may fail to detect changes in the physiologically relevant portion of the brain GABA pool located at inhibitory synapses.

Another hypothesis proposes that the primary mediator of the diet's efficacy is actually related to the changes in the energy state of the neuron. For example, ketosis leads to an increase in the ratio of ATP to ADP in the brain. This would be expected to increase the activity of the ATP-dependent sodium pumps found in neuronal and glial membranes. In neurons, this would lead to hyperpolarization and thus de-

creased excitability.<sup>89,90</sup> This has been demonstrated in rats acutely placed on food restriction,<sup>91</sup> although not directly on the diet. For glia, increased sodium pump activity would lead to improved glutamate uptake from the extracellular space, which may suppress seizures both by limiting the amount of glutamate in the extracellular space and by providing additional glutamate for conversion to glutamine, a GABA precursor. As mentioned previously, evidence for significant baseline changes in neuronal excitability or synaptic transmission is conflicting; however, changes may occur that do not significantly alter baseline properties but would prevent or reduce the expression of seizures.<sup>69</sup>

Another proposed mechanism stems from the observation that calorie restriction at levels insufficient to generate significant ketosis is still able to raise seizure threshold.<sup>55,70,92,93</sup> Calorie restriction also appears to decrease neuronal excitability. This has led to the hypothesis that a decrease in blood glucose reduces the glycolytic energy available for seizures, and that, although ketone bodies provide sufficient energy for the brain under normal conditions, their metabolism is inadequate for supporting seizures.<sup>94</sup> Additionally, calorie restriction has also been shown to decrease neuronal excitability.<sup>70</sup>

Some authors have proposed that the beneficial effects of the diet may be related to an increase in certain plasma lipids.<sup>29,95</sup> Certain free lipids, especially those referred to as PUFA or polyunsaturated fatty acids (eg, arachidonic acid and docosahexaenoic acid) have been shown to have anticonvulsant actions *in vitro*<sup>96</sup> and in animal models.<sup>97,98</sup> Recently, Fraser et al<sup>99</sup> demonstrated that serum PUFA levels are elevated in children on the diet; however, even before the induction of the diet, serum levels of arachidonic acid were well above the concentrations needed to inhibit neuronal excitability (1–20  $\mu\text{M}$ ). Furthermore, it has been shown that in adult rats on the diet, brain concentrations of PUFAs do not change significantly,<sup>100</sup> results in younger animals are not available.

There is some experimental evidence to suggest that the diet may actually have some neuroprotective effects beyond the prevention of seizures. Specifically, the diet may decrease the levels of reactive oxygen species that may contribute to neuronal damage resulting from seizures. In mice, the diet has been shown to decrease the production of reactive oxygen species, possibly enhancing the activity of mitochondrial uncoupling proteins.<sup>101</sup> In rats, there is an increase in antioxidant activity in the hippocampus, likely due to increased levels of glutathione peroxidase.<sup>102</sup> Such neuroprotective effects may explain the experimental observation that when the diet was initiated 2 days after the epileptogenic stimulus (kainic acid-induced status epilepticus), it was more effective in preventing seizures than the diet initiated after 14 days.<sup>103</sup>

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*Clinically, it remains to be determined who is the ideal candidate for the diet, taking into consideration the effects of age, seizure types, and comorbid conditions.*

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## UNANSWERED QUESTIONS AND FUTURE DIRECTIONS

Despite widespread clinical acceptance of the diet and extensive, ongoing experimental work, several basic questions in both arenas remain. It is important to acknowledge the reasons why, after more than 80 years of clinical use, so many questions remain about the diet. Because of its restrictive nature and the difficulties in performing traditional double-blind, placebo-controlled trials, it has not been possible to test the diet in a manner similar to current anticonvulsants. Thus, one must rely on, at best, prospective clinical trials (possibly randomized) and animal experiments.

Clinically, it remains to be determined who is the ideal candidate for the diet, taking into consideration the effects of age, seizure types, and comorbid conditions (which is especially important if the diet is to be used in older patients, including adults). Also, traditionally the diet has been used for patients in whom seizures are considered intractable with few, if any, other options for treatment. Because of its efficacy and relatively good side effect profile, however, the diet may be a useful therapy even in patients for whom other options are available but who have a lower likelihood of success or worse side effects (eg, infantile spasms).<sup>47</sup>

Before this step can be taken, it is crucial to define more clearly the long-term effects of being on the diet. Although long-term clinical exposures to the diet have been reported, this has typically been in patients with devastating seizures in which the improvement in their quality of life and development provided by improved seizure control would likely compensate for any long-term negative effects of the diet. But even for this group of patients, it is important to determine the long-term effects of the diet on growth and development so that they can make informed decisions. Long-term data are also needed to determine the clinical consequences of known side effects such as hyperlipidemia. Moreover, as mentioned previously, several aspects of the diet's implementation remain in question (ie, fasting, fluid restriction, and calorie restriction), and these variables may not be fully optimized. Preliminary efficacy of a diet with no calorie or protein restriction (modified Atkins diet) further raises questions about ideal factors.<sup>104</sup>

Lastly, both for clinical reasons and to advance our understanding of epilepsy, it is important to understand the mechanisms responsible for the efficacy of the ketogenic diet. This understanding will not only help optimize the diet and its application, but may also lead to novel pharmacologic treatments for epilepsy and possibly even neuroprotection.

## CONCLUSION

The ketogenic diet, an old therapy for epileptic seizures based on ancient observations of the efficacy of starvation for controlling seizures, is enjoying growing popularity in the modern era, largely due to its demonstrated clinical efficacy in diminishing seizures that respond poorly to other epilepsy treatments (medications and surgery). Recent and ongoing research is defining further the characteristics of patients who will benefit most from the diet, as well as optimizing the diet itself for maximal efficacy and minimal side effects, but much remains unknown, including long-term side effects on growth and development. In addition, research into the mechanisms responsible for the diet's efficacy are advancing our understanding of epilepsy and will, hopefully, offer new options for the future management of this disorder.

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