Most practicing child neurologists possess a basic understanding of the ketogenic diet, which is a high-fat, low-protein, low-carbohydrate diet for treating children with epilepsy who do not respond to or cannot tolerate drugs. This diet mimics the biochemical changes associated with starvation and induces, among other changes, production of ketone bodies (mainly beta-hydroxybutyrate, and to a lesser extent, acetoacetate and acetone), which have been implicated in the mechanisms of seizure control.

Before the historic first announcement of results with the ketogenic diet by the Mayo Clinic, bromides and phenobarbital were the only effective options for antiepileptic therapy. Fasting as a method for controlling epilepsy had been reported sporadically long before this time. However, it was only after such reports in the clinical journals that other medical centers began adopting the ketogenic diet as an effective treatment for intractable cases of epilepsy.

Still, the diet remained generally underutilized—mainly employed at institutions such as the Mayo Clinic and Johns Hopkins—until the 1990s, when a national television program aired a report on a child whose epilepsy was cured by the ketogenic diet. Later, the Charlie Foundation (named after the young patient) was formed and a television movie recounting another young boy’s success with the ketogenic diet was produced. The movie prompted a flood of inquiries to pediatric neurologists and epileptologists about this treatment option.

Today, after a long history of clinical use and the recent surge of professional interest and research, many questions remain unanswered about the ketogenic diet. The purpose of this review is to update neurologists by highlighting key issues and controversies pertaining to this important diet-based therapy for epilepsy. In particular, the review will focus on the potential role of ketone bodies in energy metabolism and in seizure control, the indications and contraindications for the ketogenic diet in pediatrics, and other practical clinical questions involving efficacy, patient selection, monitoring, and side effects.

### DIET OVERVIEW

The classic ketogenic diet starts with a period of

---

**THE KETOGENIC DIET IN PEDIATRIC EPILEPSY**

---

**Jong M. Rho, MD**
fasting and relative dehydration aimed at achieving ketosis, which is reflected by elevated ketone levels in the urine. This theme has several variations, such as the medium-chain triglyceride or MCT diet, all based on the principle that use of fatty acids and ketones as the main sources of energy can be forced, decreasing the utilization of carbohydrates. This important diet initiation step is usually accomplished in a hospital or specialized outpatient setting. An example of the dietary regimen after this introductory phase is listed as follows:

- Restrict total calories to 75% of the recommended daily allowance, with 90% of these calories coming from fat
- Restrict protein to 1 g/kg and provide a very small amount of carbohydrate to 10% of total calories
- Restrict fluid intake to 60 to 70 mL/kg/day
- Supplement this diet with vitamins and minerals

The target for the overall ratio by weight of ketogenic foods (fats) to antiketogenic foods (carbohydrates and protein) is usually 4:1 or 3:1. Maintaining such a high ketogenic potential usually entails a diet of fatty foods, creams, and specialty oils. A dietitian or a nurse with special nutrition training is required to tailor ketogenic diets for children and to help families adhere to the exacting regimen. Also, before being placed on the diet, the child with intractable epilepsy should always be evaluated in a childhood epilepsy center. Only a thorough evaluation in such a setting will ensure that surgical or pharmacologic treatments with potentially greater success rates are not overlooked.

Most treatment centers keep the child on this diet for 2 to 6 months to assess potential efficacy. If the patient is seizure-free, as with anticonvulsant therapy, the therapy continues for at least a 2-year period. With success, the patient can then be weaned from the diet. There is clinical evidence to suggest that early intervention with the diet may even alter the processes of epileptogenesis and render a cure permanently. However, if a patient is taken off the diet (thus breaking ketosis) and seizures recur, regaining control after reinitiation of the diet may be difficult because of a persistence of high insulin levels that result from the long period of lowered glucagon. Therefore, caution is recommended in prematurely removing patients whose symptoms are being successfully controlled.

**INTERMEDIARY METABOLISM AND KETONE BODIES**

Elevated levels of ketone bodies have been strongly associated with seizure control and seizure freedom, and neurologists always use them as biochemical markers of treatment. However, the ketosis produced by the ketogenic diet may not be the main factor in controlling epileptic seizures in children. Nevertheless, the clinical goal has historically been to achieve high urine ketone levels, and the importance of this time-honored practice can only be appreciated through an understanding of intermediary metabolism.

When the glycolytic pathway is deprived of glucose, as during starvation or the ketogenic diet, free fatty acids are mobilized as substrates for mitochondrial oxidation (Figure 1). In addition, certain amino acids may be converted to ketoads (eg, alanine to pyruvate) that can provide other substrates for Krebs cycle activity. The hepatic microsomal system can also...
convert fatty acids to dicarboxylic acids (via omega oxidation). These dicarboxylic acids require carnitine esterification for urinary secretion. Free fatty acids are not readily available to the neuron itself. However, fatty acids can undergo a series of conversions and translocations to produce acetate substrates for ketone body production. These ketone bodies are carried across the blood-brain barrier (BBB) by a fasting-inducible transporter called the monocarboxylic acid transporter and into the neuron where they are available as an energy substrate for cerebral metabolism.

Thus, a major physiologic role for ketone bodies is to provide an alternative energy substrate for brain and muscle under conditions of fasting or a high-fat diet. In a classic study of fasting obese volunteers, for example, glucose utilization accounted for only 29% of the brain’s oxygen consumption while ketones accounted for 52%.

Playing another major physiologic role, ketone bodies act as the principal source of energy during early postnatal development. Further, they are the substrates for the carbon skeleton of lipids that comprise the cell membranes of growing brains and organs. Thus, ketones are involved in both the energy supply and lipid biosynthesis of the embryonic central nervous system (CNS).

But do ketone bodies exert a direct antiepileptic effect? Can they modulate neuronal excitability? Several clinical studies, with the most recent ones being discussed later in this paper, have shown that diet-induced ketosis, especially at very high concentrations, seems to correlate with the level of seizure control. Abrupt loss of seizure control has long been known to occur within hours after ketosis is broken. Thus, the question remains of whether ketones are responsible for anticonvulsant activity, or are they just an epiphenomenon of some other diet-induced physiologic change? These issues have been explored in varied experimental settings.

One recent animal study showed that ketone bodies do not directly alter excitatory or inhibitory hippocampal synaptic transmission. Neither beta-hydroxybutyrate nor acetoacetate affected whole cell currents evoked by glutamate, kainate, or gamma-aminobutyric acid (GABA) in cultured hippocampal neurons. The ketone bodies also failed to prevent spontaneous epileptiform activity in the hippocampal-entorhinal cortex slide seizure model. Results of research performed in our laboratory using cultured mouse neocortical neurons were similar, with no effects of the ketone bodies on the classic neuronal targets of anticonvulsants. Investigators should be aware that beta-hydroxybutyrate is a stereoisomer, with the D-isomer being the biologically relevant species. The non-physiologic L-isomer possesses anticonvulsant activity both in vivo and in vitro, and is due to the presence of a contaminant, dibenzylamine.

Similarities in the chemical structures of beta-hydroxybutyrate and GABA have led to speculation about GABAergic inhibition induced by the ketogenic diet. Results from studies are conflicting, with one showing no changes in whole brain GABA and another demonstrating that ketones can increase GABA in synaptosomes. Finally, magnetic resonance spectroscopic techniques have shown elevated levels of cerebral ketones in patients who are successfully controlled by the ketogenic diet.

Overall, the experimental evidence supporting a direct link between ketones and seizures is far from convincing. Indeed, as with the underlying causes of the seizures themselves, the ameliorating actions of the ketogenic diet may be multiple, with a host of diet-influenced metabolic changes acting in concert to decrease membrane excitability.

As research continues, the clinical connection between peripheral ketone levels and seizure control still impels clinicians to confront more practical questions. For example, what assay method should be employed to monitor diet efficacy? Urine dipsticks are commonly used for this purpose, but these measure acetoacetate, the less prominent ketone body. Which ketone body actually correlates best with seizure control is unknown. If beta-hydroxybutyrate is actually...
the preferred marker, a new reflectance meter (KetoSite™, GDS Diagnostics) will assay the D-isomer from a small drop of blood. Even with these methods, the questions remain: what is the therapeutic concentration for either of these ketones, and what does the peripheral level predict about the brain level?

Clearly, many questions remain about the physiological relevance and the practical utility of monitoring ketone bodies in the ketogenic diet.

**SPECIAL INICATIONS AND CONTRAINDICATIONS**

Several specific inborn errors of metabolism can upset mitochondrial function and lead to dysfunctional glycolysis. Children with these special conditions may be strong candidates for the ketogenic diet, which will provide an important alternative energy source capable of crossing the BBB and sustaining cerebral energy metabolism.

The best example of such a condition is the family of glucose transporter defects (e.g., GLUT-1 deficiency) where glucose cannot penetrate the BBB. Two other conditions with less clear indications for special diet are pyruvate dehydrogenase complex deficiency, where acetyl CoA (coenzyme A) production is blocked, and glycogen-sparing phosphofructokinase deficiency. The benefit of the ketogenic diet is even less certain in mitochondrial cytopathies due to complex I deficiency, which presents in infancy with hypoketogenic hypoglycemia and hepatomegaly.

Most inborn errors of metabolism involving mitochondrial transport or fatty acid oxidation are absolute contraindications for the ketogenic diet. These include, for example, deficiencies in carnitine (primary or secondary), carnitine palmitoyltransferase 1 or 2, and translocase. The most common fatty acid disorder to be vigilant for is medium-chain acyl dehydrogenase (MCAD) deficiency. Other such deficiencies include those of long-chain acyl dehydrogenase, short-chain acyl CoA dehydrogenase, long-chain 3-hydroxyacyl-CoA, and medium-chain 3-hydroxyacyl-CoA.

Clues to an inborn error of metabolism include developmental delay, hypotonia, exercise intolerance, and easy fatigability. In children with these presenting symptoms, several tests can determine if the child is

<table>
<thead>
<tr>
<th>Study</th>
<th>Diet</th>
<th>Seizure Free Patients</th>
<th>Seizures ↓ by 50%</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorington 1994*</td>
<td>Classic</td>
<td>73% (controlled)</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Schwartz 1989†</td>
<td>Classic</td>
<td>46%</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>(n = 59)</td>
<td>Mod MCT</td>
<td>37%</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>(n = 59)</td>
<td>Mod MCT</td>
<td>41%</td>
<td>3 months</td>
<td></td>
</tr>
<tr>
<td>Kinnman 1992*</td>
<td>Classic</td>
<td>29% (50-99%)</td>
<td>31 months</td>
<td></td>
</tr>
<tr>
<td>Swink 1991*</td>
<td>Classic</td>
<td>22%</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>(n = 20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freeman 1998*</td>
<td>Classic</td>
<td>7%</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>(n = 75)</td>
<td>Intermittent fast</td>
<td>20%</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>Vining 1998†</td>
<td>Classic</td>
<td>10%</td>
<td>12 months</td>
<td></td>
</tr>
<tr>
<td>(n = 51)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MCT: medium-chain triglycerides.

<table>
<thead>
<tr>
<th>Table 2. Side Effects of the Ketogenic Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible long-term effects of high fats (cholesterol, triglycerides)</td>
</tr>
<tr>
<td>Growth retardation associated with protein deficiency</td>
</tr>
<tr>
<td>Vitamin and mineral deficiencies</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Kidney stones</td>
</tr>
<tr>
<td>Elevated uric acid production</td>
</tr>
<tr>
<td>Impaired immune defenses (possibly related to neutrophils)</td>
</tr>
<tr>
<td>Metabolic acidosis</td>
</tr>
<tr>
<td>Liver failure</td>
</tr>
</tbody>
</table>

| Table 1. Clinical Efficacy of the Ketogenic Diet |
suitable for the ketogenic diet. In addition to routine laboratory studies such as liver function tests and complete blood count, the recommended biochemical screening tests are for urine organic acids, serum amino acids, and serum lactate and pyruvate. As implied in Figure 1, findings of highly elevated dicarboxylic acids in the urine signal a problem with the normal pathway of intermediary metabolism (either mitochondrial cytopathy or a fatty acid oxidation defect), which warrants further investigation.

CLINICAL QUESTIONS

The ketogenic diet is highly effective in some children, but efficacy rates have varied depending on the study. Results from large prospective multicenter trials using either the classic Hopkins diet or the modified medium-chain triglyceride (MCT) oil diet are listed in Table 1.14-19 In general, more recent studies have reported lower rates of seizure control, probably due to better tracking of dropouts (ie, intention-to-treat analysis) and longer follow-up periods. Overall, about one third of children come close to seizure freedom on the ketogenic diet, one third have reductions in seizure frequency, and one third do not respond. In recent prospective, multicenter studies, only 10% actually become seizure-free.18-19

Despite generally high efficacy rates in these children who are unresponsive to drugs, many questions about the ketogenic diet require further study. Determining which seizure types respond best to the diet, for example, has been a subject of debate for decades. The early controversy centered on efficacy in treating cryptogenic versus idiopathic seizures.20-21 More recently, despite some reports of efficacy in both partial and generalized seizures,15,18 many patient types, such as those with partial seizures arising from temporal lobe pathology, still appear relatively resistant to the diet's effects. In fact, patients with partial seizures have been excluded from most studies assessing the clinical efficacy of the ketogenic diet.

Other remaining points of controversy include the benefits of the classic diet versus the modified MCT oil diet, the potential of vagal nerve stimulation as a therapeutic alternative in these drug-refractory patients, the long-term developmental effects of restricted protein and calories, and the effect of age on efficacy. On this last point, note that the diet has historically been considered more effective in infants and children because ketone extraction from periphery to brain is more efficient in the developing brain. The clinical data with the ketogenic diet in adults is sparse, with approximately half the patients responding with greater than 50% seizure reduction.22

The potential adverse effects of the ketogenic diet are well known (Table 2). In recent years, the clinical literature has focused on nephrolithiasis, constipation, growth retardation, and the potential for cardiac disease. Some of the acute toxic effects can be serious and careful monitoring is required.

Because many children with intractable epilepsy are taking valproic acid, the potential exacerbation of drug side effects by the diet becomes another key issue. In particular, because carnitine deficiency is well documented with valproic acid use, supplementation is recommended in documented cases of deficiency (ie, plasma free carnitine less than 20 µmol/L after the first week of life or an esterified to free ratio of more than 0.4).

The ketogenic diet also increases the risk of nephrolithiasis, a risk that may increase in patients taking carbonic anhydrase inhibitors such as acetazolamide or, potentially, with newer broad-spectrum anticonvulsants, such as topiramate and zonisamide, that act in part on this same enzyme. Preliminary experience indicates that children can be treated safely with such agents combined with the ketogenic diet.

In summary, although its mechanism of seizure control is imprecisely defined and several practical details of therapy (such as patient selection) require further study, the ketogenic diet remains a valuable option for therapy in the most drug-resistant cases of pediatric epilepsy. Before initiating a trial of the ketogenic diet, the clinician must ensure that the patient has had adequate trials of at least 2 or 3 anticonvulsants and has been carefully considered for potential epilepsy surgery or vagus nerve stimulation. A thorough diagnostic metabolic workup and a frank evaluation of the family's potential to comply with the diet are also mandatory. In carefully selected patients without other options, the ketogenic diet can provide major benefits, both in terms of seizure control and quality of life.

QUESTIONS & ANSWERS

Why not just use the Atkins diet? Isn't that ketogenic?
**Dr. Rho:** Many different diets are variations on the ketogenic theme but we simply do not have the clinical data to say which works best.

**Dr. Morton:** We also need to counsel patients who have initiated this diet on their own. Just because the do-it-yourself Atkins book is available at local bookstores, and it’s talked about in a keto chat room doesn’t make it safe. Ketosis on this diet doesn’t suggest efficacy. Unmonitored, there are risks, such as hyperkalemia when ingesting carbohydrates.

**Is the vagus nerve stimulator replacing the ketogenic diet as an option for children who are not traditional surgical candidates?**

**Dr. Rho:** To some degree, that was our experience at the University of Washington in Seattle. The overall use of the ketogenic diet at several major centers has fallen somewhat in the past few years.

**Dr. Bourgeois:** It depends on the seizure type. At Children’s Hospital in Boston we still prefer the ketogenic diet for those with Lennox-Gastaut and similar epilepsies. The VNS [vagal nerve stimulation] might be considered for those few children with partial seizures who are not surgical candidates, but overall our use of the ketogenic diet has stayed about the same.

**What is the role of the family in success of the ketogenic diet?**

**Dr. Rho:** The diet involves an exacting formulation and regimen, and the family and social structure of the patient is critical to its success. If the family cannot help maintain complete compliance, ketosis cannot be achieved. Even small lapses such as not eating the whole meal (to maintain the proper ratio) or eating substances that contain sugar (whether a candy bar or a whole meal) can undermine the diet. Family support is critical in maintaining a child on this diet.

**REFERENCES**