Diet therapy in refractory pediatric epilepsy: increased efficacy and tolerability

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ABSTRACT – Since the resurgence of the ketogenic diet (KD) in the mid 1990s, this diet has been used worldwide for the treatment of refractory pediatric epilepsy, including in Asian countries. However, the KD is not a convenient therapy, especially because the customary diets of Asian countries contain substantially less fat than traditional Western diets. In addition, there are various complications associated with the diet that should be considered. Unfortunately, no international protocols have been developed with the exceptions of the Johns Hopkins Hospital protocol adopted by a substantial number of hospitals. While the Hopkins protocol has been the basic model, several revisions of the initial protocol have been suggested. Changes to the applicable ages, seizure types, etiologies, the initiation of the diet, the ratio of constituents to reduce the fat content, the duration of the diet, and revised formulae, such as ketogenic milk or the all-liquid KD, have attempted to extend the indications of the KD and increase its tolerability and palatability. Recently, less restrictive KDs, including a modified Atkins diet and low-glycemic-index treatment, have been clinically tested. Here, we review these approaches toward a safer and more convenient therapeutic diet for refractory pediatric epilepsy.

Key words: diet therapy, ketogenic diet, a modified Atkins diet, low-glycemic-index treatment, refractory pediatric epilepsy

Fasting as a treatment for epilepsy was described in the New Testament of the Bible, and the earliest scientific approach was by Rawle Geyelin in the 1920s (Geyelin, 1921). In the following decades, fasting and the use of the ketogenic diet (KDI) were eclipsed as phenytoin, and then other anticonvulsants, became available. However, the varied adverse effects of such medications should be considered, especially since more than 30% of epilepsy remains intractable, despite the development of new anticonvulsants (Kwan and Brodie, 2000). In 1994, clinicians returned to using the KD following the results obtained from the Johns Hopkins Hospital (Swink et al. 1997). Since its resurgence in the mid 1990s, the KD has been used throughout the world, including in Asian countries, and is recognized as a valuable adjunct therapeutic modality (Kossoff and McGrogan 2005).
The classic KD non-fat-to-fat ratio of 1:4 necessitates a regime that is high in fat, adequate in protein (1 g/kg per day), and low in carbohydrates (Freeman et al. 2000). The medium-chain triglyceride (MCT) diet or modified MCT diet increases the palatability of the KD and is substantially more ketogenic than the classic KD but less used as it often causes gastrointestinal troubles (Huttenlocher et al. 1971, Schwartz et al. 1989). There is no difference between these three diets regarding the efficacy of seizure control (Schwartz et al. 1989).

Many reports on the efficacy of the KD have shown similar outcomes. After 12 months on the KD, about 50% of patients remained on the diet, 30%-70% of patients showed a reduction in seizure frequency of more than 50%, and 10%-20% were seizure-free (Thiele, 2003, Kang et al. 2005). The efficacy of the diet was maintained after 3-6 years on the diet (Hemingway et al. 2001). Although the efficacy of the KD is not maintained in all patients after they discontinue the diet, beneficial effects persist in most patients relative to their symptoms during the pre-KD period (Hemingway et al. 2001, Kang et al. 2005). The widespread acceptance of the KD has ended the debate about its efficacy. Despite this, many families and physicians are reluctant to initiate the KD because of its inherent difficulties, especially in Asian countries (15-30% fat, 7-20% protein, and 55-70% carbohydrate by weight in children), where the staple food is rice, and customary diets contain substantially less fat than traditional Western diets (25-35% fat, 10-30% protein, and 45-65% carbohydrate by weight in children) (Paik, 2005, Trumbo et al. 2002).

The potentially serious complications of an unbalanced diet should also be considered. Some adverse events occur within a few days or a month of commencing the diet, although others may occur after several months (table 1) (Kang et al. 2004, Lyczkowski et al. 2005, Freeman et al. 2006). Most events are transient or can be controlled with regularly scheduled assessments (table 2) (Kang et al. 2004, Klepper et al. 2004) and conservative management. Rare, life-threatening complications, such as cardiomyopathy, serious infections, or aspiration pneumonia leading to respiratory distress, should be carefully monitored for during follow-up (Kang et al. 2004). Current thinking focuses on making the KD a safer and more comfortable diet therapy while anticipating an improved outcome and prognosis when the diet is discontinued.

We will now review the efforts made to extend the use of the KD and to enhance its tolerability and safety.

### Initial and suggested protocols of the classic ketogenic diet

#### Initial Johns Hopkins Hospital protocol

According to the original Johns Hopkins Hospital protocol for the classic KD (table 3) proposed about 10 years ago (Vinning, 1998, Freeman et al. 2000), the KD was considered appropriate for all children aged from one to 15 years, with intractable seizures of any type and due to any cause, who had not responded to a variety of regimens. Exclusion of infants and adolescents older than 15 years from the diet was recommended. Families were

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**Table 1. Early- and late-onset complications of the ketogenic diet.**

<table>
<thead>
<tr>
<th>Early- and late-onset</th>
<th>Late-onset</th>
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<tbody>
<tr>
<td>Gastrointestinal disturbances*</td>
<td>Growth retardation</td>
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<tr>
<td>Dehydration†</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Infectious disease‡</td>
<td>Exacerbation of gastro-esophageal reflux</td>
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<tr>
<td>Sepsis</td>
<td>Mineral deficiencies</td>
</tr>
<tr>
<td>Lipoid aspiration pneumonia</td>
<td>Vitamin deficiencies</td>
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<tr>
<td>Hepatitis</td>
<td>Osteopenia</td>
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<tr>
<td>Acute pancreatitis</td>
<td>Renal stone</td>
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<tr>
<td>Biochemical disturbances</td>
<td>Cardiomyopathy</td>
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<tr>
<td>Abnormal lipid profiles§</td>
<td>Prolonged Q-T interval</td>
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<tr>
<td>Symptomatic hypoglycemia¶</td>
<td>Iron deficiency anemia</td>
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<tr>
<td>Persistent metabolic acidosis</td>
<td>2nary hypocarnitinemia</td>
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<tr>
<td>Hypoproteinemia</td>
<td>Optic neuropathy</td>
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<tr>
<td>Repeated hyponatremia</td>
<td>Basal ganglia injury</td>
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<tr>
<td>Hyperuricemia</td>
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<td>Hypomagnesemia</td>
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* Nausea/vomiting, diarrhea, constipation, loss of appetite. † A body weight reduction of over 5% of the baseline and marked dry skin or mucous turgor with increased urine specific gravity of over 1.020. ‡ Pneumonia, cystitis, nonspecific febrile illness. § High triglyceridemia, high cholesterolemia, low high density lipoproteinemia. ¶ <40 mg% of blood sugar with nausea, lethargy, perspiration, dizziness, tachycardia and pale appearance. (Adapted from Freeman and Kang).
advised to decrease carbohydrates markedly for two days before admission. An initial period of fasting with fluid restriction for about two days was then undertaken in the hospital and the KD was gradually introduced. A brief hospitalization for 3-7 days was also recommended to give parents and children extensive instructions on how to calculate and prepare the diet, identify potential sources of error in administering the diet. A non-fat-to-fat ratio of 1:4 was recommended to induce deeply ketotic states. The total duration of the diet was anticipated to be about three years, including a tapering-off period of one year (table 3).

| Pre-diet | 
|---|---|
| Metabolic workups* (lactate, urine organic acid and plasma amino acid assay, plasma acylcarnitine profiles) urine ALA and PBG† |  |
| 0,1,2,3,4 days and monthly | Blood ketone, blood sugar (every 12 hours for 4 days) |
| 0,3 days and 1,3,6,12,18,24 months | CBC with platelets, BUN/creatinine, liver profiles§, electrolytes with tCO₂, calcium/phosphorus/alkaline phosphatase, magnesium, uric acid, lipid profiles§, urinalysis, PT/PTT, urine ca/urine creatinine |
| 0,6,12,24 months | Blood AED levels, abdominal ultrasonography, echocardiography |
| Intermittently | plain X-ray on wrist, if needed, bone densitometry, bone enzyme profiles¶ |
| Urine ketone¶ |  |

| Table 2. Scheduled assessments to screen medical contraindications and evaluate complications of the classic ketogenic diet. |

| Indicated ages | Clinicians have hesitated to prescribe the KD for infants because it is difficult to institute and maintain ketosis in younger babies (Vinning, 1998). Furthermore, problems with hypoglycemia seem to occur more frequently in patients less than 12 months old (Vinning, 1998). In particular, neonates and young infants have low lipase activity, making them less tolerant of a high-fat diet than older children (Hamosh, 1981). To overcome these limitations, liquid ketogenic milk consisting mainly of MCT, which can be digested without lipase activity, may be used (Kang et al. 2005). The all-liquid KD, which is prepared by mixing and liquidizing all the constituents, can be given to infants, and to handicapped children if necessary, via a gavage tube or gastrostomy (Kossoff et al. 2004). The all-liquid formula is palatable, with a taste similar to that of most other infant formulae (Kossoff et al. 2004), and the efficacy of the diet in infants and its lack of significant side effects have been reported by several groups (Nordli et al. 2001, Kossoff et al. 2002, Eun et al. 2006). In adolescents, an unpalatable diet may cause resistance and poor compliance, and a lower ability to extract ketones from the blood into the brain can be a barrier to its effectiveness (Williamson, 1985). However, the maintenance rate and efficacy of the KD did not differ between adolescents and younger children (Coppola et al. 2002, Mackenzie et al. 2003, Kang et al. 2005). Recently, to increase the tolerance in older children and adolescents, a revised KD, including a modified Atkins diet and low-glycemic-index treatment, is suggested to replace the conventional KD (Kossoff et al. 2006, Pfeifer and Thiele, 2005). The positive attitudes of doctors and parents seem to be the most important factor in maintaining the diet. |

| Indicated and contraindicated seizure types and etiologies | The efficacy of the diet does not differ with the type of seizure or epileptic syndrome (Freeman et al. 1998). It has been reported that an early, dramatic response to the KD is more likely in patients with infantile spasms than in patients with complex partial seizures (Than et al. 2005). The KD is not efficacious in patients with early infantile epileptic encephalopathy or early myoclonic encephalopathy (Kang et al. 2005). Although the KD can be effective in severe myoclonic epilepsy in infancy (Caraballo et al. |
2005), it does not completely control seizures in most patients. This is because convulsive seizures usually occur in febrile illnesses, even during the diet (Kang et al. 2005).

The relapse rate after discontinuation of the KD seems to be higher in patients with complex partial seizures and symptomatic etiologies (Kang et al. 2005).

Curative surgery is sometimes required to treat refractory pediatric epilepsy with a resectable epileptogenic focus, but does not always produce a favorable outcome (Nancy et al. 2001). The KD can be offered to poor surgical candidates, or may provide a respite while the patient is evaluated for surgery (Hemingway et al. 2001, Nordli et al. 2001). In particular, malformations of cortical development, which are the most common cause of epilepsy in pediatric patients for whom surgery is indicated, may respond particularly well to the KD (Than et al. 2005), and a biological basis for improved responses may be found (Crino and Chou, 2000, Morris, 2005). However, we should consider the more frequent relapse after discontinuation of the KD in patients with symptomatic etiologies, and the restrictive nature of the KD for over 3 years. Epilepsy surgery need not be delayed to institute a trial of the KD in a patient who is a candidate for focal resective surgery (Kang et al. 2005, Kang et al. 2006a).

One of the possible mechanisms underlying the efficacy of the KD is an increase in cerebral energy production, because the KD ameliorates certain types of energy-metabolism disorders associated with defects in the use of glucose substrates, such as glucose-transporter defects and pyruvate dehydrogenase deficiency (E1) (Vivo et al. 1991, Wexler et al. 1997).

In contrast, the KD may be lethal in patients with any of several underlying metabolic diseases, including pyruvate carboxylase deficiency, fatty acid oxidation defects, 3-hydroxy-methylgluraryl Co-A lyase deficiency, and acute intermittent porphyria (Vivo et al. 1977, Nordli, 2001, Freeman et al. 2006). The KD is also known to promote metabolic stress in mitochondrial respiratory chain (RC) complex defects, and its use was typically avoided in such cases (Nordli, 2001, Freeman et al. 2006). However, similar to the effects seen in cardiovascular disease models, a KD results in increased energy availability for the synthesis of ATP, which in turn leads to a 28% increase in the efficiency of ATP hydrolysis (Veech, 2004). Furthermore, treatment with ketone bodies causes “heteroplasmic shifting”, not only between cells (i.e., intercellular selection), but also within cells (i.e., intracellular selection) (Santra et al. 2004). These findings point to the potential use of a KD to treat patients with respiratory chain complex defects. Clinically, we have encountered several patients with mitochondrial respiratory chain Complex I or IV deficiency who improved dramatically.

Table 3. Comparison between the initial protocol of the mid 1990s and our recently suggested protocol.

<table>
<thead>
<tr>
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<th>Initial protocol</th>
<th>Suggested protocol</th>
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<tr>
<td>Indicated ages and seizure types and etiologies</td>
<td>All children aged 1 to 15 years, with intractable seizures of any type and from any cause</td>
<td>All children, regardless of age and type of epilepsy or epileptic syndrome, and etiologies except for those with a well-demarcated epileptic focus or with a contraindicating underlying metabolic disease such as PCD, FAOD, 3-hydroxy MLD or AIP. Can be recommended to patients with RC complex enzyme defects.</td>
</tr>
<tr>
<td>Initiating the diet</td>
<td>An initial period of fasting with fluid restriction for about two days was undertaken in hospital prior to gradual initiation of the KD.</td>
<td>No initial fasting or fluid restriction, with only a gradual increase in calories.</td>
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<tr>
<td>Nonfat-to-fat ratio of the KD</td>
<td>Nonfat-to-fat ratio of 1:4 was recommended.</td>
<td>Nonfat-to-fat ratio of 1:3 or 1:3.5 can be tried at first, with adjustment to a 1:4 ratio according to the level of ketosis and the seizure or EEG outcomes, especially for infants. A modified ketogenic diet such as a modified Atkins diet or low-glycemic-index treatment may be recommended, especially for older children and adolescents.</td>
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<tr>
<td>Duration of the diet</td>
<td>About three years, including a tapering-off period of one year.</td>
<td>A short-term trial for about 6-12 months including a 2-4 month tapering-off period can be considered, focusing on infants with cryptogenic epileptic encephalopathy and infantile spasms.</td>
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PCD = pyruvate carboxylase deficiency; FAOD = fatty acid oxidation defect; MLD = methylgluraryl Co-A lyase deficiency; AIP = acute intermittent porphyria; RC = respiratory chain; KD = ketogenic diet.
without side effects, on the KD (Kang et al. 2005, Kang et al. 2006b), and we have recently extended our experience to patients with Complex II deficiency (unpublished data).

It has been suggested that the KD might be effective for patients with Lafora body disease, since promotion of the utilization of ketones instead of glucose by the brain might reduce glycogen synthesis and polyglucosan accumulation, thereby slowing down the progression of the disease (Minassian, 2001). A pilot study in five patients who were already symptomatic for Lafora body disease was unsuccessful, but a group from Italy anticipates that the KD will slow disease progression, especially in genetically diagnosed, pre-symptomatic siblings of Lafora disease patients (Cardinali et al. 2006).

Initiating the diet
Some clinicians believe that the KD can be initiated in an outpatient clinic and that this may improve its acceptability, subsequent maintenance, and compliance (Vaisleib et al. 2004). Although this is possible, most centers prefer initial hospitalization, believing it is necessary to observe the patient closely and to educate the family about the diet (Freeman et al. 2006).

Initial fasting was recommended to control seizures by rapidly inducing ketosis and metabolic adaptation to the ketogenic state (Freeman et al. 2000, Vinning, 1998). A period of fasting can also provide an opportunity to screen the child for any severe hypoglycemic predisposition or underlying metabolic disorder (Freeman et al. 2000, Nordli et al. 2001, Vinning, 1998). However, initially fasted and non-fasted patients do not differ in the onset of ketosis, in the incidence of complications such as hypoglycemia, or in the efficacy of seizure reduction (Kim et al. 2004).

Our experiences have shown that metabolic adaptation is satisfactorily induced with an initial stepwise caloric increase for three days without fasting (Kim et al. 2004, Vaisleib et al. 2004). Dehydration can reduce the transportation of ketone bodies into the brain and restrict the supply of this essential fuel source (Haymond et al. 1982, Haymond et al. 1983), and dehydration is less frequent in patients treated without initial fasting than in those with initial fasting (Kim et al. 2004). Recently, a prospective, randomized clinical trial suggested that gradual initiation of the KD without fasting results in fewer adverse events and is better tolerated overall while maintaining efficacy (Bergqvist et al. 2005). Most patients with rare underlying metabolic diseases can be identified before the diet is commenced by laboratory analyses and clinical characteristics (table 2) (DeVivo and DiMauro, 1999). The period of fasting with fluid restriction is emotionally and physically difficult, and by avoiding an initial fasting period and fluid restriction, hospitalization can be reduced or omitted (Kim et al. 2004, Vaisleib et al. 2004).

Nonfat-to-fat ratio of the KD
A nonfat-to-fat ratio of 1:4 should be maintained to achieve an elevated ketone level. However, a ratio of 1:3 or 1:3.5 is allowed for children younger than 15 months to increase the protein content and the tolerability of the KD (Kossoff et al. 2002). Even in older children, a nonfat-to-fat ratio of 1:3 can be tried initially, and if the ketosis achieved is insufficient to produce satisfactory seizure reduction, then the ratio can be subsequently increased to 1:4 (Nordli et al. 2001, Kang et al. 2005). Recently, modified KDs with higher carbohydrate/protein and lower fat than the conventional KD, such as a modified Atkins diet (60% fat, 30% protein, and 10% carbohydrate by weight) or a low-glycemic-index treatment (60-70% fat, 20-30% protein, and 10% carbohydrate by calorie), were shown to be effective and well tolerated in children with intractable epilepsy, even with low level of blood ketones (Pfeifer and Thiele, 2005, Kossoff et al. 2006). These authors suggested that the presence of marked urinary ketosis appeared to be less important than commonly reported for the KD.

Our experience using a modified Atkins diet was somewhat different. Specifically, we found that consistent and very marked ketosis was still important to maintain the efficacy of the diet (unpublished data). These novel diet therapies are discussed in more detail below.

Duration of the diet
Why is the KD maintained for two years with an additional year for tapering off? It is possible that this protocol was originally based on data for anticonvulsant drugs and has been determined somewhat arbitrarily. Recently, there is growing evidence that metabolic tolerability may become a problem after 2-3 years on the diet (Freeman et al. 2006). If it is necessary to maintain the KD, for example in glucose-transporter defects, the diet can be continued for over 3 years (Klepper et al. 2005). However, we need to consider the following points. The KD has more potent anticonvulsive effects than anticonvulsants and has a possible antiepileptogenic effect (Sankar, 2004). However, in infants younger than three years (the most appropriate period for the KD), the central nervous system is maturing very rapidly, and we should not ignore the considerable complications caused by an unbalanced diet, as demonstrated in long-term trials (Kang et al. 2004). Recently, a diet of liquid ketogenic milk given to two Korean infants with West syndrome in a short-term trial of about eight months (including a two-month tapering-off period) was very successful (Kang et al. 2006c). On the basis of these considerations and our anecdotal experience, a prospective clinical trial has been conducted in which eligible infants are randomly assigned to either the classic long-term KD protocol or a short-term liquid ketogenic milk regimen.
Modified Atkins diet and low glycemic index treatment

The Atkins diet was created in the 1970s by the late Dr Robert C. Atkins as a means to combat obesity (Atkins, 2002). It recommends a restricted intake of carbohydrates, initially less than 20 g/day, taken mainly as salad greens and other non-starchy vegetables, and an unlimited intake of protein and accompanying fat (Foster et al. 2003). This diet seems to have anticonvulsive effects similar to those of the KD. The Atkins diet can be commenced without a fast or hospital admission and is anticipated to have fewer side effects (Kossoff 2004). It is a more balanced diet (60% fat, 30% protein, and 10% carbohydrate by weight) than the KD (80% fat, 15% protein, and 5% carbohydrate by weight) and can be recommended as a replacement for the KD in patients for whom the KD has proved too restrictive (Stafstrom 2004). Ketosis, when attained, typically occurs within days and can be maintained with a reduction in carbohydrates to less than 10 g/day (Kossoff et al. 2003). The first formal prospective study was recently reported and attested to the effectiveness of a modified Atkins diet for epilepsy. Importantly, 80% of the patients were able to stay on the diet, 65% had a > 50% response, and 19% became seizure-free after 6 months (Kossoff et al. 2006). These results showed a striking similarity to large prospective and retrospective studies of the conventional ketogenic diet (Hemingway et al. 2001, Freeman et al. 2006).

In addition, Pfeifer and Thiele recently tried a low-glycemic-index treatment, with more liberal total carbohydrate intake but restricted to foods that produce relatively little increase in blood glucose (glycemic index < 50), and 10 of 20 patients treated with this regimen experienced a greater than 90% reduction in seizure frequency (Pfeifer, 2005). The low-glycemic-index treatment is substantially similar to a modified Atkins diet, but it can provide more carbohydrate and protein (60-70% fat, 20-30% protein, and 10% carbohydrate by calorie). These authors also reported that the presence of marked urinary ketosis appeared to be less important than commonly reported for the KD (Pfeifer, 2005, Kossoff et al. 2006).

A study of a modified Atkins diet performed at our institute [unpublished data] assessed 14 children aged 2-15 years with intractable epilepsy. Three patients had previously found the KD too restrictive, while the other eleven had never tried any dietary therapy for epilepsy. Four patients are now seizure-free, after remaining on the Atkins diet for a mean period of 7.5 months (± 3.0 months). The ability of these patients to tolerate the modified Atkins diet was encouraging, suggesting that this diet can sometimes replace the conventional KD, especially in older children and adolescents. Serious complications were rare. However, contrary to previous reports, a modified Atkins diet was not as effective overall as the conventional KD, and long-term complications require further determination. In addition, the extent of ketosis was not always proportionately correlated with better seizure outcomes. In most patients on the modified Atkins diet, the lower ketosis was not sufficient to completely control intractable seizures, and patients who showed unfavorable seizure outcomes had wider fluctuations in blood ketones. Maintenance of a steadier and higher level of ketosis is considered important to obtain favorable seizure outcomes from diet therapy. Although a further long-term follow-up of a randomized and prospective trial of these novel diet therapies is required, these diets introduce the possibility of a less restrictive diet therapy, and are expected to become an additional or adjunctive therapy for refractory pediatric epilepsy.

Summary

Our recommended protocols for a safer and more convenient diet therapy, and for extending the indications, are as follows; the KD is indicated for all children with intractable epilepsy, regardless of age, type of epilepsy or epileptic syndrome or etiologies, except for those with a well-demarcated, resectable epileptic focus or with a recognized, contraindicative underlying metabolic disease, such as pyruvate carboxylase deficiency, fatty acid oxidation defect, 3-hydroxy-methylglutaril Co-A lyase deficiency, or acute intermittent porphyria. The KD can also be recommended in patients with respiratory chain complex defects. Brief hospitalization for 3-7 days is recommended but can be omitted for the initiation of the non-fasting KD and for a modified Atkins diet. The diet begins without initial fasting or fluid restriction but with only a gradual increase in calories. A greater than usual water intake is recommended to prevent kidney stones. A nonfat-to-fat ratio of 1:3 can be tried initially, especially in young children, to increase the protein content and tolerability of the KD. The diet can then be adjusted to a 1:4 ratio depending on the level of ketosis, and seizure or EEG outcomes. For infants with epileptic encephalopathy and infantile spasms, a short-term trial of the diet for about 6-12 months, including a 2-4 month tapering-off period, can be considered. The ability of the patients in this study to tolerate the modified Atkins diet was encouraging, suggesting that this diet can replace the conventional ketogenic diet, especially in older children and adolescents. Serious complications were rare. However, these are preliminary results, and long-term complications require further determination.

Conclusion

Although the beneficial effects of the KD were confirmed in the 1930s, diet therapy was eclipsed by newly developed, more convenient anticonvulsants. Even now, the
KD is not easy to maintain, and we require an alternative diet therapy that is safer and more convenient while maintaining efficacy. This review covers several suggested modifications, though, unfortunately these have remained controversial, and randomized and prospective studies are rare. Several randomized studies are now being initiated, including double-blind protocols. Novel diet therapies providing higher protein, more carbohydrate and less fat than the conventional KD, look promising. Even newly developed anticonvulsants do not attain the efficacy of the KD, and we should continue our endeavors to develop a safer and more convenient diet therapy that can be extended to more patients with refractory epilepsy.

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