

# More fat and fewer seizures: dietary therapies for epilepsy

Eric H Kossoff

The ketogenic diet is a high-fat, adequate protein, low carbohydrate diet that has been used for the treatment of intractable childhood epilepsy since the 1920s. The diet mimics the biochemical changes associated with starvation, which create ketosis. Although less commonly used in later decades because of the increased availability of anticonvulsants, the ketogenic diet has re-emerged as a therapeutic option. Only a decade ago the ketogenic diet was seen as a last resort; however, it has become more commonly used in academic centres throughout the world even early in the course of epilepsy. The Atkins diet is a recently used, less restrictive, therapy that also creates ketosis and can lower the number of seizures. Dietary therapies may become even more valuable in the therapy of epilepsy when the mechanisms underlying their success are understood.

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Patients with epilepsy have more therapeutic choices than ever. Over the past decade the number of available anticonvulsants has more than doubled and the newer drugs have fewer side-effects, drug interactions, and less teratogenicity. Even older drugs are now available in liquid, chewable, and intravenous preparations with extended-release forms and fewer doses per day are needed. If drugs do not work, surgery can be offered and leads to seizure freedom in many cases. In cases where surgery is not an option, a vagal nerve stimulator (VNS) can be implanted.<sup>1,2</sup> With all these therapies available, why would any patient with epilepsy need to change their diet to control seizures?

The ketogenic diet is a restrictive high-fat, low-protein, and very low-carbohydrate diet mostly given to children. Meals must be carefully chosen, with amounts of foods measured, so eating outside the home at schools or in restaurants can be difficult. For some children, even the smallest of carbohydrate indiscretions (including medications or even systemically-absorbed sunscreen) can lead to more seizures. Not all epilepsy centres offer dietary therapy as it requires a specially trained dietitian and medical team and is often poorly reimbursed. For decades, this diet was seen as unhealthy, potentially dangerous, and scientifically unsound.

Why, therefore, would any physician or parent want to try the ketogenic diet? First, the ketogenic diet has probably fewer side-effects than anticonvulsants, and many of them are treatable and reversible.<sup>3</sup> Second, its efficacy is likely higher than anticonvulsants for children with intractable epilepsy, and there are spectacular cases of seizure freedom

that have captured media attention. By no means “alternative”, the ketogenic diet is still perceived as a more natural and less expensive approach by many families. In addition, although many new anticonvulsants have been developed, most have only been available for a few years, and paediatric experience is limited. The ketogenic diet has been in continuous use for nearly a century. Lastly, when faced with the uncertainty and irreversibility of surgery for intractable epilepsy, the ketogenic diet can always be attempted as a last resort and, if unsuccessful, discontinued. For all these reasons, the popularity of the ketogenic diet has increased substantially worldwide.

## History

The idea that epilepsy could be cured by diet was first proposed as a “water diet”—initially described by Rawle Geyelin in 1921 based on the work of Michigan paediatrician Hugh Conklin and faith healer Bernarr Macfadden—in which children would be fasted for as long as 3 weeks.<sup>4,5</sup> Dr Wilder first described the use of a maintained diet to mimic this starvation (high fat and low carbohydrate) that same year.<sup>6</sup> It is essentially the same ketogenic diet that is in use now, 83 years later. Until 1938, the ketogenic diet was one of the few available therapies for epilepsy, but the development of phenytoin and other anticonvulsants made the diet seem outdated and unnecessary. For many decades, the ketogenic diet was used only at a few academic centres until public interest was rekindled in 1994.<sup>7</sup> At that time, a boy named Charlie was treated at our institution for intractable epilepsy that had failed to respond to multiple drugs and even surgery.<sup>8</sup> To date, he remains seizure and medication free. His story, and the creation of the Charlie Foundation, has led to resurgence in the diet’s popularity and an increase in research (figure 1).

## What is the ketogenic diet?

The ketogenic diet provides nutrition with 1 g/kg protein and 5–10 g of carbohydrate per day, with the remainder of calories (usually 75% of the recommended daily allowance) as long-chain triglycerides.<sup>9</sup> Meal plans are carefully tailored by a nutritionist for each individual patient. The ratio of fat

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EHK is at The Johns Hopkins Medical Institutions, Baltimore, Maryland, USA.

**Correspondence:** Dr Eric H Kossoff, Jefferson 128, The Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, MD 21287-1000, USA. Tel +1 410 614 6054; fax +1 410 614 2297; email [ekossoff@jhmi.edu](mailto:ekossoff@jhmi.edu)

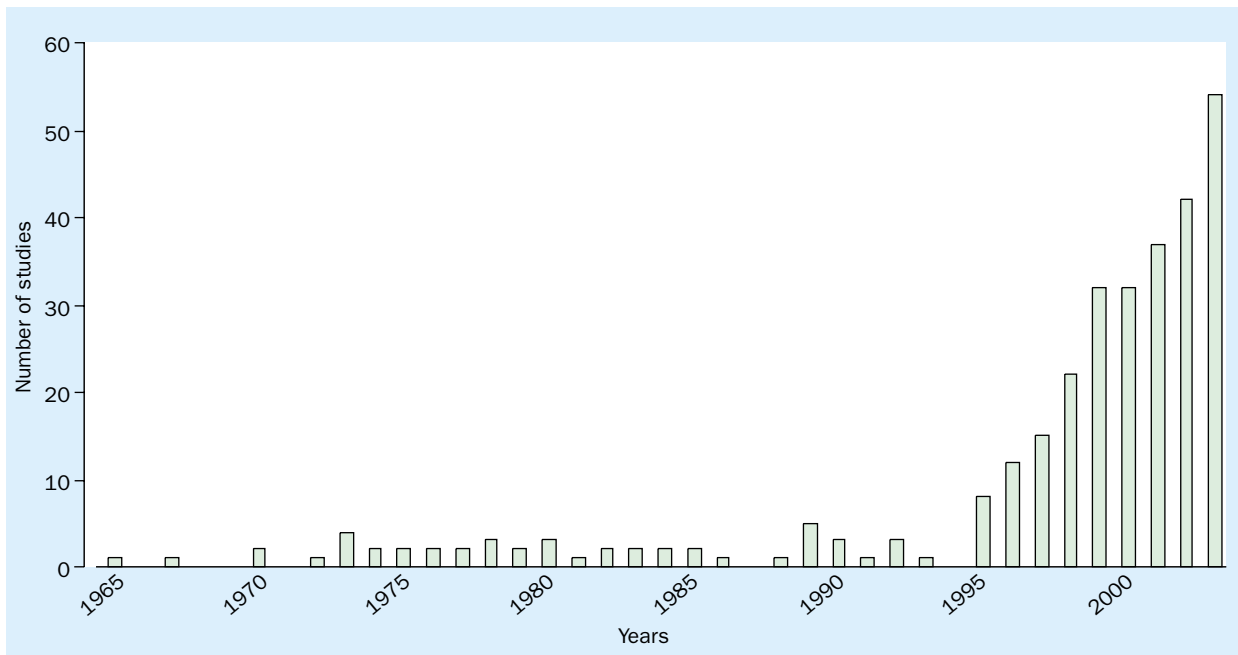


Figure 1. Clinical studies of the ketogenic diet 1965–2003.

to carbohydrate and protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive and possibly more effective. Meals can be quite palatable, including bacon, eggs, tuna, shrimp, vegetables, mayonnaise, and sausages (figure 2). It is perhaps easiest to give the diet to formula-fed infants and patients fed through a gastrostomy tube, because it can be prepared as a liquid preparation—eg, Carbohydrate-Free,<sup>TM</sup> Mead Microlipid,<sup>TM</sup> and Polycose<sup>TM</sup>.<sup>10</sup> In addition, SHS International has created a pre-prepared, powdered, 4:1 ketogenic diet formula, although this is not available worldwide at this time.

The use of the medium-chain triglyceride (MCT) rich diet is quite similar in efficacy.<sup>11</sup> This diet is theoretically more palatable; however, bloating is a common complaint. A multicentre study in the UK, headed by Dr Helen Cross at Great Ormond Street Hospital in London, comparing the

two diets is currently underway. The diet can be provided in many different cultures, religions, and food practices (panel 1) worldwide with several different high-fat foods including 36% heavy whipping cream, butter, MCT oil, sesame or peanut oil, ghee, and Orley Whip (South African product).

Children are admitted to the hospital for 5 days in which the ketogenic diet is slowly advanced after a 24–48 h fast (panel 2).<sup>9</sup> There is some evidence to indicate that a fast is unnecessary for long-term efficacy.<sup>12</sup> However, we still find it valuable to monitor patients on admission, watch for acute worsening on the diet, educate families, and complete any aetiological assessment. The immediate benefit occasionally seen with fasting can be very reassuring and families have a potential clinical tool to quickly increase ketosis in the future if necessary.<sup>13</sup> Parents tend to be universally more concerned about the fast than the children and are surprised by how easy it is. However, hypoglycaemia (serum glucose <30 mg/dL) during the fast can occur and be symptomatic. We tend to give 30 ml of orange juice in those situations with a follow-up glucose check in 1 h. Drug regimens are not changed for 3–6 months, although we have found an earlier tapering can be safe.<sup>14</sup> Routine use of magnesium, zinc, vitamins D and C, B-complex vitamins, and calcium is recommended.



Figure 2. 4:1 ratio lunch for a child age 6 years.

### How does the diet work?

The mechanism of action by which the diet suppresses seizures is controversial.<sup>15</sup> The most likely factor is increased formation of ketone bodies.<sup>15</sup> Ketone bodies (beta-hydroxybutyrate, acetoacetate, and less prominently acetone) are created by the liver metabolism of body fat in a response to diminished glucose (figure 3). Ketones are an efficient source of energy for the body and the brain. Ketosis

can be measured in both serum and urine, providing a marker for seizure control.

How or if ketone bodies suppress seizures is not known, but studies have shown protection in mice against electroshock and bicuculline.<sup>16</sup> Ketones are also structurally similar to GABA and may have direct anticonvulsant or even antiepileptogenic effects.<sup>17</sup> Other investigators have theorised that calorie restriction, weight loss, and acidosis may also play a part in seizure control, but further investigation is needed.<sup>18–21</sup> The diet may also improve cerebral energy reserves and concentrations of mitochondrial uncoupling protein.<sup>22–24</sup>

### Who is helped by the diet?

Most patients in our population are 5–10 years of age with long-standing, intractable Lennox–Gastaut Syndrome or another mixed epilepsy syndrome.<sup>25,26</sup> The ketogenic diet is effective independent of factors such as age, seizure type, and EEG pattern.<sup>26</sup> Patients with gastrostomy tubes may be the most ideal candidates.<sup>10</sup> In addition, the diet can be used for patients who are not refractory to other treatments, although the time and commitment can be considerable when compared with drug therapy.<sup>27</sup>

The ketogenic diet's value for patients not in the typical age range (5–10 years old) has recently been shown. Both infants and adolescents can do well and maintain the diet for long periods.<sup>28–30</sup> A poster at the American Epilepsy Society in December 2003 described the use of the ketogenic diet in 26 adults, with 46% having a >50% reduction in seizures.<sup>31</sup> Although no long-term side effects were identified, cholesterol concentrations increased from a mean of 207 mg/dL to 253 mg/dL and a mean weight loss of 6.7 kg also occurred.

There are several disease states in which the ketogenic diet is not only beneficial, but may be life saving. The two main disorders are glucose transporter protein deficiency (GLUT-1) and pyruvate dehydrogenase deficiency.<sup>32,33</sup> Other disorders—such as pyruvate-carboxylase deficiency, defects of fatty-acid oxidation, carnitine deficiency, and possibly some of the mitochondrial disorders—are thought to be contraindications to the ketogenic diet.<sup>9</sup>

One disorder that requires more investigation is infantile spasms. 23 infants who had mostly not responded to drugs such as corticotropin and vigabatrin were treated with the ketogenic diet.<sup>30</sup> About half had greater than 90% improvement over 3–12 months, including 88% of those who did not respond to corticotropin. Independent predictors of favourable outcomes included age less than 1 year and exposure to three or fewer anticonvulsants. Theoretically, the ketogenic diet would be even more beneficial as first-line therapy, and might avoid the side-effects of corticotropin, vigabatrin, and other anticonvulsants. A multicentre trial of the diet as initial therapy for infantile spasms is being planned.

### Long-term outcomes

Children on the ketogenic diet at our institution are followed up regularly in the clinic with laboratory studies (lipid profile, electrolytes, anticonvulsant levels, and urine

#### Panel 1. Sample ketogenic diet recipes (courtesy of Maria Joaquina Marques-Dias [Brazil], Dr Gabriela Wohlrab [Switzerland], Dr Janak Nathan [India], and Dr Ong Hian Tat [Singapore])

##### Switzerland

(Four to one ratio)  
6 g 35% fat cream  
20 g carrots  
11 g potato  
20 g vegetable oil  
13 g raclettekäse (cheese)

##### India

(Two to one ratio)  
34 g chicken  
40 g onion  
93 g tomato  
1 g ginger  
1 g garlic  
34 g ghee/oil or 42 g butter  
One or two cloves  
Bay leaf  
Green chilli  
Salt to taste  
Red chilli powder to taste

##### Brazil

(Four to one ratio)  
25 g skinless chicken breast  
20 g okra  
5 g green olives  
14 ml oil  
1 teaspoon of chopped coriander  
Garlic and salt

##### Singapore

(Four to one ratio)  
8 g beehoon (rice vermicelli)  
17 g boiled lean pork  
20 g cabbage, green, boiled,  
33 g sesame oil

concentrations of calcium and creatinine) every 6 months. Parents are advised to check weights and urine ketones at least twice a week and to maintain frequent email or telephone consultation with our group. At this time we do not recommend routine testing of serum beta-hydroxybutyrate, but one study indicated it is a more accurate guide to seizure control.<sup>34</sup> Drugs for these patients should only be managed by the centre implementing the diet.

The diet's efficacy has been assessed in several studies.<sup>7,25,26,35–37</sup> The largest series of 150 children showed that after 1 year on the diet 50% had a >50% seizure reduction, and 27% specifically had >90% improvement.<sup>26</sup> When followed up for an additional 3–6 years, the benefits lasted even after the diet was discontinued; with 44% having >50% improvement.<sup>35</sup> Compared with results of most anticonvulsant drugs, which provide a 30–40% chance of >50% improvement in add-on trials, the diet's efficacy is apparent. Because many patients placed on the ketogenic diet have not responded to more than three anticonvulsants,

**Panel 2. Ketogenic diet protocol at Johns Hopkins Hospital****Day before admission**

Low carbohydrate consumption for 24 h  
 Children examined in clinic the afternoon before admission  
 Fasting starts in the evening

**Day 1**

Admitted to the hospital  
 Fasting continues  
 Fluids restricted to 60–75 cc/kg  
 Blood glucose monitored every 6 h  
 Use carbohydrate-free drugs  
 Parents begin educational programme

**Day 2**

Dinner given as a third of calculated diet meal as “eggnog”  
 Blood glucose checks discontinued after dinner  
 Parents begin to check urine ketones periodically

**Day 3**

Breakfast and lunch given as a third of diet  
 Dinner increased to two-thirds (still eggnog)  
 Education programme completed

**Day 4**

Breakfast and lunch given as two thirds of diet allowance  
 Dinner is first full ketogenic meal (not eggnog)

**Day 5**

Full ketogenic diet breakfast given  
 Prescriptions reviewed and follow-up arranged  
 Child discharged to home

the efficacy is even more significant. A double-blind, placebo-controlled trial (glucose versus saccharin solution given during the initial fasting period) of the diet for Lennox–Gastaut syndrome with multiple seizure types has been completed and is being analysed. This study will be one of the few to formally study the effects of the ketogenic diet prospectively.<sup>25,26,37</sup>

The ketogenic diet may have other benefits. The money saved through the use of fewer drugs and revised care can be significant.<sup>38,39</sup> Behaviour has also been reported to be improved in children with epilepsy both with and without autism.<sup>40,41</sup>

**Side-effects**

There are common, uncommon, and rare side-effects of the ketogenic diet.<sup>3</sup> Common side-effects include lack of weight gain (often planned), acidosis (worse with illness), and constipation. Less common are kidney stones (6%), growth inhibition (more significant at young ages), and hyperlipidaemia.<sup>42–44</sup> The risk of kidney stones does not seem to be increased by the additional use of acetazolamide, topiramate, or zonisamide—anticonvulsants that independently increase the risk of kidney stones by 2–4%.<sup>45</sup> Children had an increase in their cholesterol, triglyceride, and low-density lipoprotein concentrations from the 75th to the 99th percentiles after 3 months.<sup>43</sup> The increase in cholesterol may be caused by ketogenic-diet induced decrease in apolipoprotein B, the major serum carrier of cholesterol. The changes tended to plateau after 6 months

and normalised when the diet was stopped. Adjustments to the diet (eg, increased protein and polyunsaturated fats) can be made in children with significantly high lipid concentrations. The long-term results of these side-effects have not been adequately studied, but few children at our centre have had to discontinue the diet because of them.

Rare (case reports only) side-effects include cardiomyopathy, prolonged QT syndrome, vitamin and mineral deficiencies, pancreatitis, basal ganglia injury, and bruising.<sup>46–51</sup> We have not seen these complications in our 500 patients and do not routinely screen for them. A recent study in rats that were given the diet for 1 month introduced concerns about cognition and brain growth, although these concerns have not been raised by any study of human beings.<sup>52</sup>

**Discontinuation of the diet**

Children are kept on the ketogenic diet for as long as it is beneficial, but typically 1–2 years if it is successful. Half of the patients at our centre are on the diet for 1 year, but discontinue earlier if it is deemed ineffective or too restrictive.<sup>26</sup> Similarly to anticonvulsants, the diet is tapered over several months by lowering the fat to protein and carbohydrate ratio, then slowly relaxing restrictions on weighing foods and measuring carbohydrate intake. The replacement of high-fat cream with whole milk and eventually with skimmed milk can be used to discontinue the diet more rapidly. When families feel the diet is not effective any longer, it can be tapered slowly while seizures are monitored.

**The Atkins diet**

The Atkins diet was created in the 1970s by the late Dr Robert C Atkins as a means to combat obesity;<sup>53</sup> like the ketogenic diet, it encourages fat intake, restricts carbohydrates, can induce weight loss, and has been avoided in medical research.<sup>54,55</sup> The Atkins diet can create ketosis if carbohydrates are reduced sufficiently, it does not restrict protein or calories, can be started without a fast or hospital admission, and may have fewer side-effects. In general, the ketogenic diet is 80% fat, 15% protein, and 5% carbohydrate; whereas the Atkins diet is 60% fat, 30% protein, and 10% carbohydrate. Unlike the ketogenic diet, ready-made Atkins products are now available in many groceries and restaurants, although the actual carbohydrate content may be too high for patients with epilepsy despite advertised “net carbs”. However, it allows a child to choose items from a menu at a school cafeteria or restaurant, which is nearly impossible on the ketogenic diet. Families can buy the paperback, *Dr Atkins’ New Diet Revolution* in almost any bookstore nowadays and begin the diet at home;<sup>53</sup> although close dietary and neurological monitoring are required throughout for anyone attempting the diet.

A study done at our institute, published last year, assessed six children and adults age 7–52 years with intractable epilepsy.<sup>56</sup> This was the first formal study to describe the use of the Atkins diet for epilepsy. One patient had tried the ketogenic diet before but found it too

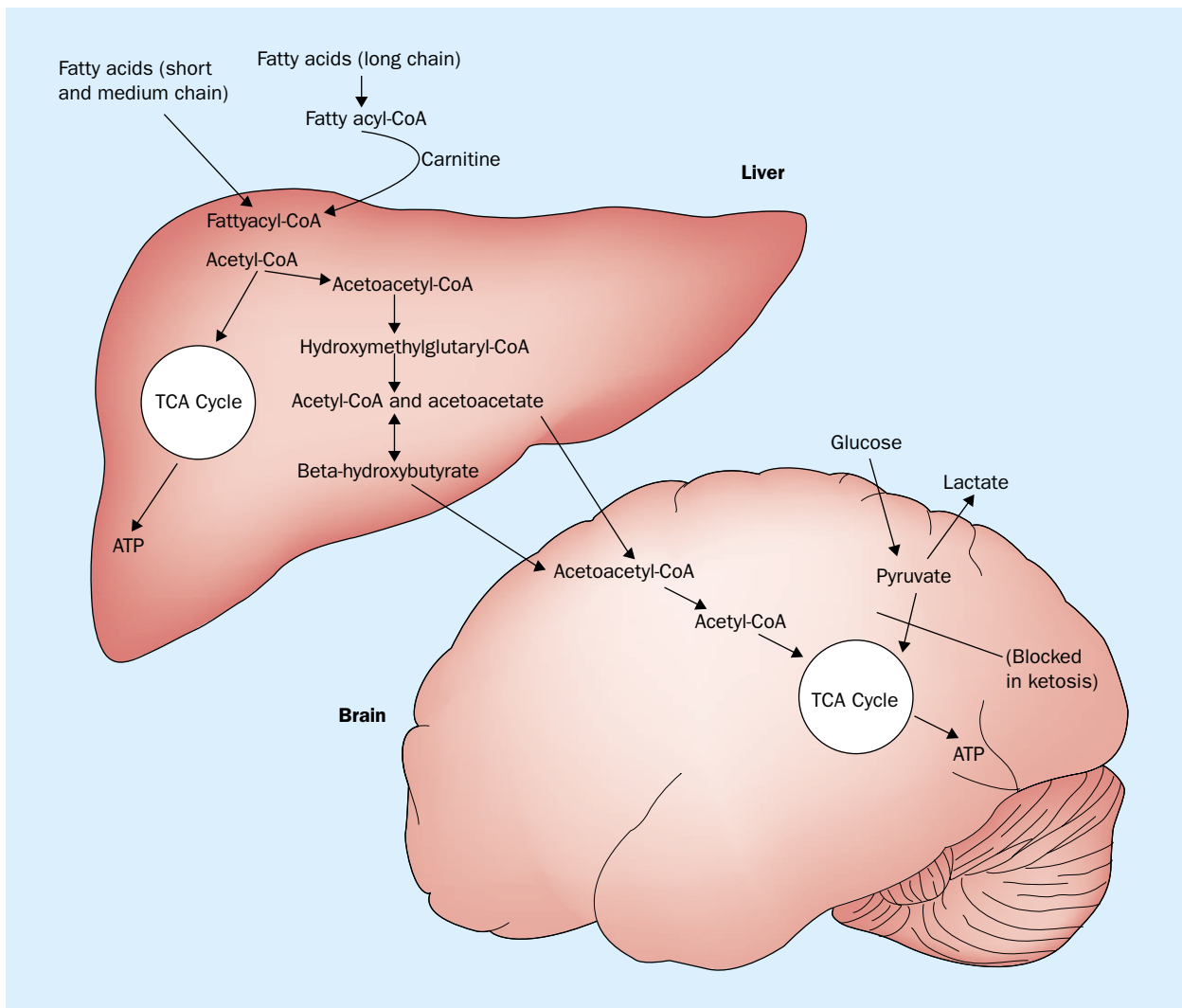


Figure 3. Liver and brain metabolism of fats into energy.

restrictive; the others had never tried any dietary therapy for epilepsy. A half of the patients are now seizure free or have only brief auras after remaining on the Atkins diet for as long as 20 months. Success tended to relate to the level of ketosis. No patient had renal stones and only two patients had hypercholesterolaemia (233 mg/dL and 245 mg/dL).

On the basis of this very preliminary evidence, a prospective trial of the Atkins diet is underway at Johns Hopkins Hospital, (Baltimore, MD, USA). Children age 3–18 years, with more than three seizures per week and who have not responded to two or more anticonvulsants are eligible. Carbohydrates are at first limited to 10 g a day; ready-made, low-carbohydrate products are discouraged, and drug regimens are not changed for the first month. A study of adults age 18 years and older is being planned at this time. We feel strongly that any dietary therapy for epilepsy should be given only if both a neurologist and dietitian monitor the patients closely. The potential risks of excessive weight loss, dyslipidaemia, and renal disease or stones mandate careful medical observation.

### Other dietary options

Could other dietary interventions also be effective? Anecdotal stories of different dietary approaches to seizure control have been reported. However, no careful studies in human beings have been done. There have been reports of children with previously subclinical coeliac disease and epilepsy responding to a gluten-free diet.<sup>57</sup> We have been in contact with a veterinarian who has successfully treated dogs with epilepsy by use of a gluten-free diet.

If calorie restriction rather than ketosis is most important, perhaps other diets (including low-fat) could be just as beneficial? It seems that some form of ketosis is necessary, but this has not been proven in human beings. The benefits of periodic calorie restriction (fasting) have been known for some time in the clinical management of the ketogenic diet, both during the initiation period and beyond if seizures cluster.<sup>9,13</sup> Perhaps periodic fasting with calorie restriction in and of itself is of value above ketosis?

Parents occasionally report improvement in seizures with decreased additives, preservatives, or stimulants

### Search strategy and selection criteria

References for this review were identified by searches of MEDLINE and Current Contents using the search terms "ketogenic", "Atkins", and "dietary therapy for epilepsy" between 1965 and 2004. References were also identified from relevant articles and through searches of my own files. Abstracts and reports from meetings were included only when they related directly to previously published work. Only papers published in English and Spanish were reviewed. The reference list was subsequently modified during the peer-review process on the basis of comments from reviewers.

(caffeine, chocolate, or sugar), but again, there is no scientific evidence to prove this. Some research into the

benefits of oral beta-hydroxybutyrate (as a supplement) has indicated its potential role, although it is somewhat unpalatable and large quantities are required to create serum ketosis.<sup>58,59</sup> All these potential dietary modifications and more may be tried in the future should patients with epilepsy continue to become frustrated with standard therapies.

### Conflicts of interest

I have no conflicts of interest.

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