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Ketogenic Diets: New Advances for Metabolism-Based Therapies

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Abstract

Purpose of review—Despite myriad anticonvulsants available and in various stages of development, there are thousands of children and adults with epilepsy worldwide still refractory to treatment and not candidates for epilepsy surgery. Many of these patients will now turn to dietary therapies such as the ketogenic diet, medium-chain triglyceride (MCT) diet, modified Atkins diet, and low glycemic index treatment.

Recent Findings—In the past several years, neurologists are finding new indications to use these dietary treatments, perhaps even as first-line therapy, including infantile spasms, myoclonic-astatic epilepsy (Doose syndrome), Dravet syndrome, and status epilepticus (including FIRES syndrome). Adults are also one of the most rapidly growing populations being treated nowadays; a group of patients previously not typically offered these treatments. In 2009, two controlled trials of the ketogenic diet were published as well as an International Expert Consensus Statement on dietary treatment of epilepsy. Ketogenic diets are also now being increasingly studied for neurologic conditions other than epilepsy, including Alzheimer disease and cancer. Insights from basic science research have helped elucidate the mechanisms by which metabolism-based therapy may be helpful, both in terms of an anticonvulsant and possibly neuroprotective effect.

Summary—Dietary therapy for epilepsy continues to grow in popularity worldwide, with expanding use for adults and conditions other than epilepsy.

Keywords

Ketogenic; diet; epilepsy; modified Atkins; metabolism; ketosis

INTRODUCTION

In the 1920s and 1930s, there were few anticonvulsants other than phenobarbital and bromides available for the treatment of epilepsy. As a result, the ketogenic diet (KD) was created in 1921 at the Mayo Clinic in Rochester, Minnesota by Dr. Wilder for children with refractory epilepsy [1]. This treatment restricted carbohydrates, protein, calories, and fluids

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CONFLICTS OF INTEREST

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while significantly increasing fat intake to comprise approximately 90% of calories. Within several years it became widely used for adults as well as children. As new anticonvulsants such as phenytoin were introduced, the popularity of the KD waned, with usage primarily limited to select academic institutions and as a last resort for children with severe epilepsy. After the creation of the Charlie Foundation parent support group in 1994, interest was reawakened in the United States and then around the world several years later [2].

We are now in an entirely new era of using dietary therapies with incredible growth and research. Nearly 100 new articles devoted to dietary therapy per year are being published. Large international symposia devoted to the use of dietary therapies have been held in Phoenix, Arizona in 2008, Edinburgh, UK in 2010, and a third is planned for Chicago in 2012. Two prospective controlled trials demonstrating efficacy of the ketogenic diet were published in 2008 and 2009, as well as an International Consensus Statement guiding ideal use [3-5**]. The ketogenic diet is initiated and managed differently around the world with evidence suggesting similar benefits no matter how this is done. In addition, there are now four different ketogenic diets available to choose from: the traditional “classic” ketogenic diet (KD), the medium-chain triglyceride (MCT) diet, the modified Atkins diet (MAD) and the low glycemic index treatment (LGIT). Diets are being used for adults and in conditions other than epilepsy. In this review, we will highlight all of these changes, including new insights from basic science research into mechanisms of action, in the past 2 years.

DIFFERENT WAYS TO PROVIDE THE DIET

For most of the history of the ketogenic diet there has been a pervasive sense of restrictiveness and rigidity in the approach to its initiation and maintenance. In the past several years, this has been radically changed as a result of new research demonstrating equivalency with several approaches. Probably the first and most influential of these studies was from Dr. Bergqvist and her group in 2005 [6]. They found that the traditional fasting period at KD onset did not improve outcomes above a “gradual” approach after 3 months in a randomized trial. It was also associated with less acidosis, hypoglycemia and weight loss.

As a result of this study, other investigators have continued to look at alternative ways to start as well as maintain the KD. Research has shown that the KD can be started as an outpatient and with lower ratios, and maintained without the same level of restrictiveness on calories, fluids, and concurrent anticonvulsants [5**]. In addition, the eventual discontinuation of the KD, similarly subject to traditional guidelines for decades, can also be individualized with similar risk of seizure recurrence [7]. This new flexibility is outlined in detail in the 2009 International Consensus Statement, written by 26 neurologists and dietitians from ketogenic diet centers worldwide [5**].

“ALTERNATIVE” DIETS

Although the KD is helpful for approximately 50% of children who try it, and even with the previously-discussed loosening of rigidity in its provision, there are many patients with epilepsy who are concerned about the difficulty in changing their lifestyle to adopt a ketogenic diet. Some of these patients include adolescents, adults, busy families with multiple children, and patients with very high baseline carbohydrate intake (or fat aversion).

For these patients, the “alternative” diets may be new options to successfully allow them to try this nonpharmacologic approach (Table 1).

The medium-chain triglyceride (MCT) diet has been used since the 1970s, using more of this highly ketogenic oil in order to free up more carbohydrates. The MCT diet was studied in a prospective, controlled, randomized manner by Dr. Neal and colleagues from London in a recent well-publicized study [4*]. They determined that the classic KD led to higher serum ketone levels, fatigue (at 3 months), and mineral deficiencies [8, 9] but no difference in growth, efficacy, and overall tolerability [10].

The low glycemic index treatment (LGIT) was first published by Dr. Thiele from Boston in 2005 with the goal of providing carbohydrates with glycemic indices <50 in order to maintain stable blood glucose levels [11]. Although serum ketones do increase, they are minimal, and it is started as an outpatient without a fast. An update in 2009 from the same group now includes 76 children, of which 50% of those remaining on the diet at 3 months had >50% seizure reduction [12]. Nearly one quarter still found the LGIT restrictive and stopped for that reason.

The fourth ketogenic diet, entitled the modified Atkins diet, was first published by our group in 2003 [13]. The MAD is also started as an outpatient without a fast, but does not restrict calories, fluid, or protein. Carbohydrates are restricted to 10 grams per day (children) or 20 grams per day (adults) and fats strongly encouraged in order to maintain ketosis. There are now 22 publications to our knowledge about the use of the MAD in children and adults, with 123 (44%) of 280 total subjects having >50% seizure reduction after 6 months of which 72 (26%) had >90% improvement. These results are quite similar to described in the KD. One recent publication suggests that using one of the KD formulas (KetoCal) during the initial month may in fact boost the efficacy of the MAD by providing additional fat sources [14*]. Children can be switched from the MAD to the KD, with 30% of those switched having additional benefit, especially if their underlying condition was myoclonic-astatic epilepsy [15]. Future directions for the MAD likely include adult use and in developing countries.

NEW EPILEPSY INDICATIONS

A decade ago, the KD was solely indicated for children with intractable epilepsy. There were no particular indications mentioned in reviews such as this one, other than perhaps GLUT-1 (glucose transporter-1) deficiency. Children with Lennox-Gastaut syndrome were the most commonly started on the KD, despite no specific evidence of benefit for that condition.

The dramatic change in this concept was very evident in the 2009 consensus statement, in which the first table of this document is devoted to “indications” for the KD [5**]. These included myoclonic-astatic epilepsy, tuberous sclerosis complex, Rett syndrome, infantile spasms, Dravet syndrome, and children receiving only formula. Continued work has demonstrated benefit for infantile spasms, and this may be the fastest growing population to be started on the KD due to its efficacy as well as ease of use with ketogenic formulas widely available worldwide. Research by Hong and colleagues in 104 consecutive infants demonstrated that 64% would have >50% spasm reduction using an intent-to-treat analysis

[16*]. Perhaps most remarkably, 37% had at least 6 months of spasm freedom during treatment. Kang and his team from South Korea randomized 40 spasm-free infants treated with the KD to either stop the diet after 8 months or after the more traditional 24 months [17]. The risk of spasm recurrence was equal between groups, and growth disturbance higher in the children treated longer, suggesting short KD periods are justified in infantile spasms [17]. The data justifying the strong benefit of the KD for Dravet syndrome [18] and myoclonic-astatic epilepsy similarly continues to grow since the publication of the Consensus Statement.

New indications continue to be studied. One exciting development has been the recent attention to the use of the KD for refractory status epilepticus. The epilepsy condition entitled FIRES (fever-induced refractory epilepsy syndrome), often difficult to control with poor outcomes, appears to be very susceptible to the KD [19*]. Providing the KD as a formula through a nasogastric tube to a patient in an intensive care unit with status epilepticus is a very feasible option, with successful results typically described within 7-10 days [19]. Prospective studies are underway. Other conditions reported as responding to dietary therapy include absence epilepsy, Sturge-Weber syndrome, and hypothalamic hamartoma [20-22].

ADULTS

Although described in the 1930s, the more recent use of the KD for adults with intractable epilepsy has rarely utilized and infrequently studied. Largely as a result of the emergence of the MAD as a less restrictive alternative, the past few years have seen a renaissance of activity in this population. Recent studies of the MAD [23] and KD [24] in 2011 have all demonstrated surprisingly high efficacy and tolerability. Evidence would suggest that when effective, the MAD will lead to seizure reduction within several weeks, thus the potential restrictiveness (if ineffective) need only be short-lived. The benefits of weight loss for obese patients with epilepsy may also be an additional valuable outcome.

PREVENTING SIDE EFFECTS

Side effects do occur with dietary therapies as these treatments are neither alternative nor designed to be healthy. However, most of the adverse effects are treatable, especially hypercholesterolemia (with ratio or fat composition changes), mineral deficiencies, acidosis, constipation, and weight loss (with extra calories). An important change in the mindset of neurologists and dietitians at ketogenic diet centers is to now prevent these side effects before they actually occur. Using alternative diets such as the MAD and LGIT may be one option. Avoiding a fasting protocol may be another [6]. Supplements such as calcium, selenium, zinc, and Vitamin D have been proposed in recent years [25, 26]. A study of oral citrates (Polycitra K) as an empiric, universal supplement to children on the KD found a reduction in the incidence of kidney stones from 6.9% to 0.9%, $p=0.02$ [26].

DISEASES OTHER THAN EPILEPSY

In a manner similar to anticonvulsants, the KD is being examined for neurologic conditions other than epilepsy. Nearly all neurologic conditions have been reported in either animal studies or limited human trials as having potential benefit, including autism, Alzheimer's

disease, migraine, hypoxic-ischemic encephalopathy, Parkinson disease, amyotrophic lateral sclerosis, and traumatic brain injury [27]. Recent years have seen three conditions studied in a bit more detail, including brain tumors, Alzheimer disease, and migraine.

Brain tumors have now been investigated in humans, based on the hypothesis that altered glucose metabolism has anti-oncologic effects. A prospective trial of a low carbohydrate diet (70 grams of carbohydrate per day limit) to 16 adults in Germany with metastatic tumors of various etiologies with no conventional therapy options remaining was recently published [28]. Five appeared to have some stability of their disease and improvement in quality of life, suggesting further study is warranted [28].

Although the results from these trials and more are uncertain, what is clear is that continued investigations into uses for ketogenic diets other than epilepsy will continue. It is likely that in those conditions for which dietary therapy is successful, the mechanisms of action may be very different from epilepsy, leading to new insights perhaps as to why these therapies work [27].

Ketogenic diet vs. fasting—As noted previously, the ketogenic diet was designed to mimic the beneficial effects of fasting. This has led most authors to believe a ketogenic diet and fasting share anticonvulsant mechanisms. This belief was addressed in a direct trial of a ketogenic diet versus an intermittent fasting regimen in mice undergoing acute seizure tests [29]. Surprisingly, the two interventions showed opposite results in the 6 Hz and kainic acid tests, demonstrating that their anticonvulsant mechanisms differ from one another in seizure-naïve mice (although both had anticonvulsant properties). Future *in vivo* and *in vitro* studies can more accurately model the respective intervention of interest (i.e., ketogenic diet versus fasting).

Ketosis vs. hypoglycemia—Another question in the literature is whether the ketogenic diet's effects are due to elevated ketone levels or low glucose levels, both of which are present in animal models of the diet (although consistently low glucose levels are not seen in patients) [30]. The glycolysis inhibitor 2-deoxy-D-glucose (2DG) appears to have a different acute seizure test profile than the ketogenic diet, indicating that merely lowering glucose levels, while weakly anticonvulsant, does not fully mimic the ketogenic diet's effects [31,32]. One of the factors necessary for the antiepileptic effect of glycolysis inhibition (e.g., 2DG) is the neuron-restrictive silencer factor (NRSF)[33]. NRSF conditional knockout mice were protected against post-kindling seizures after ketogenic diet treatment, providing further evidence that the ketogenic diet's anti-seizure effects are due to more than just glycolysis inhibition [34*].

Ketone body concentrations during the diet—One longstanding question is what concentrations of ketone bodies are achieved during ketogenic diet therapy. Prior work examined postmortem concentrations but hippocampal microdialysis catheters recently were used to measure levels of beta-hydroxybutyrate in live mice [35]. The level of beta-hydroxybutyrate in other regions of the brain (i.e., neocortex) was not measured, nor were levels of the other two main ketone bodies, (i.e., acetoacetate and acetone) but this study still should inform experimental design in future *in vitro* studies of ketogenic diet mechanisms.

Pathways, not metabolites?—Although the ketogenic diet's effects may be exerted by a direct effect of ketone bodies (possibly in combination with lower glucose levels), another possibility is that the ketogenic diet alters nutrient-integrating pathways (i.e., 'sensors' that react to changes in levels of multiple nutrients). The best known example of this is the mammalian target of rapamycin (mTOR) pathway, which reacts to changes in levels of glucose and amino acids [36]. Patients with tuberous sclerosis harbor mutations in key proteins in this pathway and pharmacological inhibition of mTOR activity decreased tumor growth and seizures in patients with tuberous sclerosis, as well as in selected animal models [37]. The ketogenic diet also lowered levels of activity in this pathway [38]. Further work should determine whether the ketogenic diet's anticonvulsant action is mediated via decreased mTOR activity.

Neurotransmitters, receptors, and channels—Ketogenic diets may exert their anticonvulsant effects via the inhibitory neurotransmitter GABA [39]. The diet's effects on the excitatory neurotransmitter glutamate have not been studied as widely. Acetoacetate (and to a lesser extent, beta-hydroxybutyrate) competitively inhibited the ability of chloride ions to allosterically activate vesicular glutamate transporters (these transporters load presynaptic vesicles with glutamate), suggesting one potential net inhibitory effect of ketone bodies is via decreased neuronal excitation [40*]. Furthermore, acetoacetate inhibited quantum glutamate release from acute hippocampal slices and in rat brains exposed (via microdialysis catheter) to the convulsant and potassium channel blocker 4-aminopyridine. The concentration of acetoacetate required to completely suppress glutamate secretion in the latter experiment was higher than predicted during a ketogenic diet (noted previously), so one question is whether similar findings would be seen after ketogenic diet treatment. Nonetheless, these data highlight the potential therapeutic importance of acetoacetate, which has not been studied as thoroughly as beta-hydroxybutyrate.

Other channels and neurotransmitters may play a role in the ketogenic diet's anticonvulsant effects. The ketone body beta-hydroxybutyrate increased baseline and activity-dependent opening of inward-rectifying K_{ATP} channels in cultured mouse dentate gyrus neurons, supporting the hypothesis that beta-hydroxybutyrate leads to inhibition of neuronal firing after recurrent neuronal activity (i.e., as in a seizure)[41]. Adenosine also may play a role in the ketogenic diet's anti-seizure effects. A ketogenic diet is ineffective against seizures in mice harboring mutations in adenosine A_1 receptors or adenosine kinase and in those treated with an A_1 antagonist [42]. Norepinephrine was shown previously to play a key role in the ketogenic diet's anticonvulsant mechanism [43,44]. The mechanism through which the ketogenic diet exerts its effects via different neurotransmitters and channels is a potentially rich area for further investigation.

Neurophysiology—One common criticism of epilepsy studies is that the intact live brain has not been examined as thoroughly as *in vitro* preparations. Juvenile rats treated with 2-3 week of a ketogenic diet did not show changes in tests of locomotor function or in a conditioned fear test, nor were there changes in electrophysiological measures of long-term potentiation *in vivo* [45]. However, a study of unanesthetized freely-moving adult rats after three weeks of pretreatment with a ketogenic diet showed decreased measures of long-term

potentiation [46]. Differences between the studies could be due to the age of the rats studied or an effect of anesthesia. These findings may be relevant not only to seizures (i.e., increased inhibition) but also on other processes such as learning, as the authors note. The relevance of this concern would be better delineated in animals with epilepsy, where the anticonvulsant action of the diet (and likely benefits on learning noted after improved seizure control in humans) can be more fairly evaluated, since ketogenic diets are not clinically used in people without some form of illness.

Mitochondria—Mitochondria are suspected to be important in the ketogenic diet's effects, given the shared location of fatty acid oxidation and cellular protection [47]. Ketogenic diet treatment decreased morphological signs of mitochondrial damage (including decreased numbers of ragged red fibers and muscle mitochondrial structural distortion) in Deletor mice, which accumulate mitochondrial DNA mutations with age [48]. Thus, a ketogenic diet may protect against conditions where mtDNA damage occurs. Ketogenic diets also may exert a neuroprotective effect through antioxidant mechanisms mediated via the NF E2-related transcription factor, although short-term effects may be different than long-term ones [49].

SUMMARY

The use of dietary therapies for children with intractable epilepsy continues to grow in popularity both clinically and from a research perspective. Recent years have seen strong interest in new indications for this treatment, new methods of initiation and maintenance, new “alternative” diets such as the modified Atkins diet, usage in adults, first-line consideration, preventing adverse effects, and basic science collaborations.

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Table 1

Comparison of the four major ketogenic diets.

	Classic Ketogenic (4:1)	Medium Chain Triglyceride (MCT)	Modified Atkins	LGIT
Fat, g (% calories)	100 (90%)	78 (70%)	70 (70%)	60 (45%)
Protein, g (%)	17 (7%)	25 (10%)	60 (25%)	40 (28%)
Carbohydrates (%)	8 (3%)	50 (20%)	10 (5%)	40 (27%)