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Review

Dietary therapies for epilepsy: Future research ☆

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ABSTRACT

Since 1921, dietary therapies have remained valuable options in the treatment of intractable childhood epilepsy. The traditional ketogenic diet has been well demonstrated, including in a recent randomized, controlled trial, as being highly effective. More recent alternative diets such as the medium-chain triglyceride diet, modified Atkins diet, and low-glycemic-index treatment have expanded the use of this modality to more children as well as adults. In this review, we discuss our top 10 most pressing research topics related to the ketogenic diet that warrant future study. As well, two promising ketogenic diet clinical researchers discuss their past and current research to help answer some of these questions.

1. Dietary treatments: A historical perspective

In 1921, Dr. R.M. Wilder from the Mayo Clinic proposed using a high-fat, low-protein, and low-carbohydrate diet to mimic the starvation state that had been reported during the same year by Dr. H. Rawle Geyelin as a treatment for epilepsy not controlled with phenobarbital or bromides [1]. Ninety years later, the use of dietary therapies has advanced considerably because of both basic and clinical research worldwide. Since Medline became available in 1965, there have been approximately 940 published human studies of dietary therapies for epilepsy. In 2008 in Phoenix, AZ, USA, and again in 2010 in Edinburgh, Scotland, much of this active research was highlighted in 4-day conferences devoted solely to dietary therapies for neurological disorders.

The ketogenic diet (KD) today appears generally similar to what children were eating in 1921: heavy whipping cream, oils, butter, eggs, meats, and mayonnaise, with limited fruits and vegetables and only minute amounts of breads, pastas, or rice. However, appearances aside, there have been considerable changes and advances in the field of KD research, sparked by the Charlie Foundation parent support group, which was created 17 years ago. Hundreds of trials across ages, seizure types, and cultures have demonstrated that approximately half of children with intractable seizures treated with the KD will have at least a 50% reduction in seizures [2]. One such trial, led by co-author Dr. Elizabeth Neal, proved the diet is effective in a randomized, controlled study design [3]. Ideal candidates for dietary treatments have been reported, including children with glucose transporter 1 (GLUT-1) deficiency, pyruvate dehydrogenase deficiency, infantile spasms, gastrostomy tubes, Rett syndrome, some mitochondrial disorders, tuberous sclerosis complex, and, by co-author Dr. Sudha Kessler, myoclonic–astatic epilepsy (Doose syndrome) [4,5]. Research has led us not only to identify the adverse side effect profile of dietary treatments, but to prevent those side effects from occurring. Attempts to make the traditional KD easier and safer to start in children have continued and have led to "alternative" diets such as the medium-chain triglyceride oil diet, modified Atkins diet, and low-glycemic-index treatment. The latter two diets especially may have a role in adults, a population with epilepsy typically not offered the traditional KD.

What will be the important research questions and unresolved clinical issues facing the field of dietary therapies in the next several years? How should KD clinical research focus its efforts to truly advance this nonpharmacological treatment for epilepsy clinically and scientifically? In this review, we provide our personal top 10 topics of KD research that we believe should be addressed initially. Dr. Kessler and Dr. Neal, two junior investigators with a bright future in this field, then discuss their current research and the future directions in which it may progress.

2. Top 10 dietary therapy research issues

2.1. Should dietary treatment be a first-line option for epilepsy?

In 2008, results from a retrospective case–control study comparing the KD with adrenocorticotropin hormone (ACTH) for treatment of

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new-onset infantile spasms at Johns Hopkins Hospital altered the conception that the KD should be used only after multiple antiepileptic drug (AED) failures [6]. To invoke this concept, KD research had first to identify the ideal candidates (such as patients with infantile spasms) [6–9]. They would also have epilepsy syndromes or specific situations (e.g., dysplasia, head trauma) in which the expected course is that of intractable medication-resistant seizures. Dr. Kessler, in her 2007 retrospective analysis of the experience with myoclonic–astatic epilepsy (Doose syndrome) at Children's Hospital of Philadelphia, also suggested that the KD was so superior to most known anticonvulsants that it "should be considered earlier in the treatment course" [5].

To use dietary therapies before an anticonvulsant regime implies that a major change in the typical KD management has occurred or will occur. KD teams (neurologists and dietitians) must be willing and ready to start the diet as emergently as is currently done with anticonvulsant drugs. Contraindications (e.g., fatty acid oxidation defects, primary carnitine deficiency, pyruvate carboxylase deficiency) must be ruled out in advance [4]. Everyone involved (including the child) must be in universal agreement: parents must be willing to allow a reasonable time for dietary therapies to prove beneficial (e.g., 2–3 weeks), insurance companies must cover the costs of the admission and potentially KD formulas, and neurologists must themselves believe strongly in the KD's chances of success. Future research should address these concerns prior to routine, first-line use of the KD and demonstrate efficacy in prospective trials versus anticonvulsants.

2.2. In what ways do ketogenic diets work in mice … and what clues does this give us for humans?

Basic science has advanced the KD field on a par with the clinical research of the past decades. No longer do we tell parents "we don't know how the KD works"; today we inform them that there are multiple likely mechanisms [10]. Mitochondrial neuronal upregulation may likely be the common pathway, which probably explains the particular benefit of dietary therapies for mitochondrial disorders [11]. Research has demonstrated that elevated free fatty acid (possibly polyunsaturated fatty acids) levels, ketosis (including acetoacetate, β-hydroxybutyrate, and acetone), caloric restriction, fasting, and reduced glucose may each be independently helpful for epilepsy [10].

It is hoped further basic science research will continue to provide clinical researchers with clues to modify or tailor KDs to be both safer and more effective. If ketones are important, then foods that increase ketone levels could be used or a ketosis-inducing supplement could be added to a child's current diet. If ketones (or fat perhaps) are not important, lower ketogenic ratios (e.g., 2:1 or 1:1) would be appropriate and the routine monitoring of serum or urinary ketosis could be eliminated. If glucose reduction is critical, then lower-glycemic-index carbohydrates and high-fat foods, which induce dyslipidemia and gastrointestinal upset, would be avoided. Should caloric restriction prove valuable consistently, then intermittent fasting or reduced-calorie normal diets could be implemented. Continued close collaboration between basic and clinical science will be critical.

2.3. What are the places of the modified Atkins diet and low-glycemic-index treatment?

First published in 2003 and 2005 respectively, the modified Atkins diet (MAD) and low-glycemic-index treatment (LGIT) were designed to mimic the KD in efficacy but in an outpatient, less restrictive approach without protein or calorie restriction [12,13]. Preliminary studies of these "alternative" diets have demonstrated an efficacy equal to that of the KD [14,15].

Eight years since the introduction of these "alternative" diets, however, there remains uncertainty regarding their potential role. For infants and those with gastrostomy tubes, the widespread ease of use and availability of KD formulas make the MAD and LGIT unnecessary. What about for the majority of other children? Should the MAD and LGIT be used initially, with the KD used only if unsuccessful? Studies suggest that a more restrictive onset to diets (lower carbohydrates and higher ketogenic ratios) may be beneficial: Are the MAD and LGIT sacrificing long-term efficacy if used initially [16,17]? What about using alternative diets afterward (e.g., start the KD and then switch to MAD or LGIT for tolerability and safety)? Are these diets truly easier or do strict dietary food calculations and Web-based KD programs (e.g., KetoCalculator) allow the KD to be just as well tolerated? What are the long-term adverse effects and efficacy of these diets? Could "alternative diets" be a possible solution for intractable epilepsy in developing countries with limited dietitian resources [18]? It is hoped that as these diets become more widely used and studied, these questions will be answered.

2.4. How can we prevent side effects (not just identify them)?

In 2011, the adverse effect profile of the KD has been largely established. Common problems include constipation, acidosis, slowed weight gain, and gastrointestinal upset [4]. Less common side effects include significant dyslipidemia, slowing of height velocity, kidney stones, and carnitine deficiency. Rare adverse effects include prolonged QT interval, increased infections, pancreatitis, selenium deficiency, and bone fractures. Most of these adverse effects can be treated without discontinuation of the KD [4].

Future studies should focus on prevention, not only identification, of adverse effects to make the KD safer for all children. Today, there is evidence that empiric use of oral citrates (e.g., Polycitra K) may prevent kidney stones, increased quantities of MCT oil and unsaturated fatty acids may be useful for dyslipidemia, and carnitine and selenium supplementation may help in these particular deficiencies [19–22]. Additional prospective studies are needed to definitively demonstrate that KD modification and supplementation with vitamins or other medications are helpful. Could these supplements be combined into a single tablet or solution to provide to children daily while receiving dietary therapies? Would more of certain foods (or less of others) prove beneficial for safety?

2.5. What are the long-term side effects of the diet, especially in those with prolonged exposure?

It is known that the risk of kidney stones, bone fractures, and diminished height increases with continued KD exposure [23]. However, at least in one retrospective questionnaire- and laboratory-based study, 6 years after discontinuation of the KD, there were neither obvious increased metabolic adverse effects nor dyslipidemia [24]. What would be the results of echocardiograms or carotid ultrasounds? Are these children at risk for heart, bone, or kidney disease at higher frequency in later adulthood? If adverse effects are found in future studies, then routine postdiet screening would be advisable (and, perhaps, would alter management while on the KD). If not, then the lack of adverse heart health effects might alleviate the fears of concerned parents and hesitant neurologists over KD initiation for epilepsy.

2.6. Can the diet be "fine-tuned" when started?

Anticonvulsants can be adjusted based on levels and clinical responses, split throughout the day, changed in formulation to liquids or tablets, and switched to generic preparations. Similarly, the KD ratio (fat:carbohydrate and protein grams), calories, fluids, and type of fats are frequently adjusted by dietitians. However, presently there is only anecdotal evidence that any of these dietary adjustments are effective in seizure control, and most published studies regarding changing ratios, adjusting calories to achieve ideal body mass index (BMI), and lowering carbohydrate daily limits after months of dietary

treatment show little evidence of seizure improvement [16,17,25]. With a therapy as carefully calculated as the KD, it is natural for parents and dietitians to want to attempt many dietary modifications, especially when seizures recur after initial improvement. A single study recently suggested that adding branched-chain amino acids to the KD might improve efficacy [26]. However, the cohort chosen had already improved to some degree with the KD. Future prospective studies are needed to carefully examine which diet modifications are beneficial. In addition, the necessity of widely available, but often expensive supplements, such as carnitine, omega-3 fatty acids, branched-chain amino acids, and MCT oil, should be clarified.

2.7. Do we have enough evidence of the efficacy of the ketogenic diet in 2011?

Despite decades of research, including prospective and multicenter trials, the view of the KD literature is not entirely flattering. A 2003 Cochrane review found "no evidence from randomized, controlled trials to support KDs" [2]. However, there are presently two randomized, controlled studies that are helpful. The first, in 2008, included 145 children and compared dietary treatment using either MCT or long-chain traditional KD with continued anticonvulsant management for 3 months [3]. It was concluded that the KD was superior to anticonvulsants ($P<0.0001$). The second study was published the following year, a randomized, double-blinded, and controlled crossover study of 20 children with Lennox–Gastaut syndrome [27]. Unfortunately, the results only trended toward statistical significance compared with "placebo" (60 g of glucose) after 6 days ($P=0.07$). The findings were felt to be due largely to either an insufficient placebo state and/or the powerful effects of two fasting periods for the initiation of the KD leading to better seizure control in both groups [27].

Are more studies required to prove "beyond a doubt" that dietary treatments are effective and for which epilepsy types or syndromes? In the meantime, insurance companies have covered the KD for years in the United States when deemed the child's appropriate next treatment. Child neurologists are offering dietary treatments at more institutions worldwide or referring to centers nearby. In addition, there is a wave of parent enthusiasm through epilepsy support groups, such as The Charlie Foundation and Matthew's Friends which help to bring the dietary treatments to media and parental attention.

There are, however, regions of the world where the KD is viewed as "alternative" and not routinely available. Most countries that offer dietary therapy have long waiting lists and limited dietitian resources. Although first-line use of the KD may be reasonable, insurance companies often require trials of at least two anticonvulsants before covering an admission for dietary services. Will additional controlled trials improve this situation? The two studies mentioned above took approximately 7–8 years each to enroll subjects and complete analysis [3,27]. Is this significant effort worth the time and money?

2.8. In this era of limited financial resources, can the ketogenic diet be started as an outpatient?

One of the most debated topics in the 2009 international expert consensus statement on the KD was the method of initiation [4]. Most experts (88%) recommended hospital admission of children for the initiation period of the KD to provide family education; manage acute hypoglycemia, acidosis, and vomiting; and observe for any potential unmasked (and previously unrecognized) metabolic disorder [4]. Importantly, 73% of the panel also believed that the KD could be started as an outpatient in "very select situations" [4].

An outpatient approach saves money, keeps the child and parents in their familiar surroundings, and decreases parental stress. Parents continue to need hospital-based education and have frequent contact during the entire process. There have been only two publications, both retrospective, that describe an outpatient initiation of the KD. These were small studies with 8 and 37 patients, respectively, but both showed outpatient initiation is feasible [28,29].

Fasting children at the start of the KD stems back to the early days of dietary therapy when it was theorized that high-fat diets mimicked the starvation state, which was known to be therapeutic [1]. The duration of the fasting period has decreased over the decades from "until ketotic" to a set period (usually 24 hours). However, a 3-month randomized trial demonstrated that a nonfasting approach led to equal seizure reduction, accompanied by less weight loss, hypoglycemia, acidosis, and need for intravenous fluids [30]. Debate still persists, with 58% of the International Ketogenic Diet Study Group believing a fast is helpful (but not necessary), 31% finding no role for fasting, and 11% believing it is necessary [4].

Clearly, more randomized prospective research is needed. Does an outpatient, nonfasting approach reduce the costs and short-term side effects yet negatively impact immediate seizure control? Do families who choose to start the KD as an outpatient require additional later education and counseling? What are the actual financial implications of an outpatient approach and do any savings translate into more salary support for ketogenic dietitians and, possibly, more children overall that can be treated?

2.9. Should dietary therapy be offered to adults?

In one of the largest prospective studies in the history of the KD, Dr. Clifford Barborka reported a 56% response rate in 100 consecutive patients with epilepsy seen at the Mayo Clinic [31]. What was striking was that the subject population included only adults aged 16 years or older. The results were deemed "sufficiently encouraging to warrant further trial" [31]. Surprisingly, the next published use of the KD specifically for adults was 69 years later [32]! Diets were relegated in the 1940s and 1950s to alternative medicine for children and perceived as less realistic for adults. Considering that up to 30% of adults with epilepsy have seizures that are intractable to medications, and many are not surgical candidates, the KD may provide a quick, reversible alternative to vagus nerve or deep brain stimulation.

The modified Atkins diet has since been evaluated by two prospective studies in adults to date, with 11 of 38 (29%) having a >50% seizure reduction after 6 months of treatment [33,34]. Each of these studies had difficulties with long-term compliance and dyslipidemia. Weight loss can occur, but may be intentional and beneficial.

These early results suggest that the KD and, perhaps in particular, the modified Atkins diet (because of its ease of use and initiation) could be reasonable options for adults who are considering a new anticonvulsant therapy but desire a therapy that is different and unique. Further research should clarify subpopulations of adults most likely to respond and remain compliant. Can these alternative diets be implemented with limited dietitian support, recognizing a general lack of adult dietitians familiar with the KD? Would adults with gastrostomy tubes respond to formula KDs similarly to children? What are the ramifications of dyslipidemia for an adult at risk for cardiovascular disease? Are diets perhaps an ideal option for women with epilepsy planning a pregnancy?

2.10. Should ketogenic diets be used for neurological conditions other than epilepsy?

One of the more recent, unique, and perhaps controversial issues being studied for KDs is their use for neurological conditions other than epilepsy [35]. Often initially investigated in animal models, several new potential uses have been reported in small pilot series for adults in the past few years. Clinical trials of KD treatment for conditions such as brain tumors, autism, migraine, and amyotrophic lateral sclerosis (ALS) have had mixed results [35]. In 2009, a powdered medium-chain triglyceride supplement was approved by

the U.S. Food and Drug Administration for the treatment of Alzheimer's disease and is now commercially available (www.axona.com) [36].

It seems inevitable that the KD will be increasingly studied for these conditions. Fascinating research questions will undoubtedly be answered in coming years. Which conditions will actually be proven amenable to dietary therapy and will the mechanisms of action be different from how the KD affects epilepsy? Will patients be willing to radically alter their diet for disorders with a chronic, progressive pattern that are unlikely to improve but may stabilize (e.g., ALS and brain tumors)? Would the modified Atkins diet be more effective and preferable to the KD for these conditions? Will pediatric neurologists and epileptologists run the trials or just act as consultants to neuro-oncologists and cognitive neurologists?

In summary, these 10 KD research issues are likely to be the most intriguing and studied over the next decade. Many more exist, especially within the basic science community. In the subsequent half of this review, Dr. Neal and Dr. Kessler discuss their own particular research and how it may address several of these important research questions.

3. Promising Areas of Research and Young Investigators

3.1. Elizabeth Neal

Toward controlled evidence and the value of the medium-chain triglycerides

The classical version of the KD employs a ratio system to calculate the macronutrient proportions in the diet, most commonly 3:1 or 4:1 (fat:protein and carbohydrate), the fat being long-chain triglyceride, provided from food sources [4]. A different version of the KD using MCT was introduced in the 1970s [37]. Differences in MCT metabolism facilitate more rapid and greater oxidation of medium-chain fatty acids, with higher ketone yield per kilocalorie of energy than their long-chain counterparts. Carnitine is not necessary for breakdown of MCT compared with long-chain triglycerides. This increased ketogenic potential means less total fat is needed in the MCT diet, allowing more protein and carbohydrate (Table 1).

Although there has been significant interest in dietary therapies in recent years, the lack of randomized trials of the KD was a concern [2], and our group set out to design such a study, with patient data collection commencing at the end of 2001 [3]. One hundred forty-five children aged 2–16 years whose seizures had failed to respond to at least two anticonvulsant medications and had at least seven seizures weekly were randomized to receive a KD, either immediately or after a 3-month delay, with no additional treatment changes (control group) [3]. Of the 73 children who were allocated to a KD and the 72 who were allocated to the control group, data on 103 were available for analysis: 54 diet, 49 control. After 3 months, the mean percentage reduction from baseline of seizure frequency was significantly lower in the diet group than in the control group (38% reduction vs 37% increase, respectively; $P<0.0001$). Three extreme outliers were included in the controls: when removed, the mean percentage of baseline seizures in this group fell to 113%, reducing the mean difference between the groups to 51%, still highly significant ($P<0.0001$). Using an intent-to-treat analysis, 28 patients in the KD group had greater than 50% seizure reduction (38%), compared with 4 controls (6%) ($P<0.0001$), and one child in the KD group achieved seizure freedom. Most frequently cited side effects at the 3-month point were constipation, vomiting, lack of energy, and hunger, none of which led to dietary withdrawal.

Table 1
Comparison of fat, protein, and carbohydrate content of the classic and medium-chain triglyceride ketogenic diets.

	Usual starting macronutrient prescription		
	Fat	Protein	Carbohydrate
Classic ketogenic diet (4:1 ratio)	90% of energy, long chain	10% of energy from protein and carbohydrate combined	
Medium-chain triglyceride ketogenic diet	30–60% of energy from MCT, 11–45% of energy from long chain	10% of energy	15–19% of energy

Results from this, the first published randomized, controlled trial of the KD, were reported in June 2008 [3]. We are aware that responder rates are higher in some observational studies previously cited, which may be due in part to the severely intractable nature of the seizures experienced by children included in our trial because of the perception that the KD was a "last resort" treatment in the United Kingdom at the time of recruitment. Also, it is possible there was selection bias in some other cohort studies, and our trial did not include children under the age of 2, who are known to respond favorably to the KD [7,8].

As part of our trial design, the diet group included children randomized to both classic and MCT protocols. Despite a previous nonrandomized trial showing no difference in efficacy between these two KD protocols [37], the question of which diet may be better for a child was frequently raised in clinical practice. The MCT diet is widely used in the United Kingdom; however, this is not true in the United States, perhaps for reasons of perceived intolerability (gastrointestinal upset with the MCT diet). We found no difference in efficacy between these two types of KD at 3, 6, or 12 months [38]. There were no significant differences in tolerability between the diets except increased reports in the classic group of lack of energy after 3 months and vomiting after 12 months. We were able to conclude from this part of our trial that both diets have their place in the treatment of childhood epilepsy.

Secondary outcome measures from our trial were growth and nutritional status. Impaired growth, especially in younger children, is a known risk of KD treatment [39–41]. We also found that *Z* scores for both weight and height fell during KD treatment; however, there was no difference in outcome by 12 months between children on the classic diet and those on the MCT diet, despite the increased protein in the latter [42]. The analysis of nutritional indicators, including carnitine, is still in progress. Preliminary results on plasma vitamins A and E, zinc, selenium, and magnesium suggest that micronutrient status may be suboptimal in this group, with particular concern about changes in levels of vitamins A, E, and magnesium [43].

Having completed the randomized, controlled trial, in what directions does our research go now? Our study did not include infants, and the design of a randomized trial including, or limited to, this age group would be useful in determining whether the KD should be used earlier in the treatment of very young children with epilepsy. It is also unknown how long children should remain on dietary therapy. Two newer diets have recently also been shown to be extremely successful in the treatment of seizures: the modified Atkins diet and the low-glycemic-index treatment [12,13]. Currently, resources are scarce in the United Kingdom, and availability of dietary therapies is subject to regional variation. Answers to these questions will help prioritize limited dietetic services in this area of work and so maximize their benefit to the children who most need them.

4. Promising Areas of Research and Young Investigators

4.1. Sudha Kessler

Toward identifying the ideal candidate for the ketogenic diet

A persistent challenge in epilepsy care has involved understanding how to direct specific therapies toward individual patients. This question is particularly salient when considering the KD, an intervention that requires substantially more effort than administering medication, but also holds considerable promise of benefit in children whose seizures have been medication resistant. Traditionally, KD initiation has been delayed until six or more antiepileptic drugs (AEDs) have failed [30,44,45]. However, current definitions of intractable

epilepsy specify failure of adequate trials of two to three AEDs, because of the precipitous drop in the likelihood of becoming seizure free with subsequent AED attempts [5]. In the consensus opinion of the International Ketogenic Diet Study Group, the KD may be reasonably presented as a treatment option after failure of two AEDs [46]. A greater number of children might be offered KD treatment earlier in the course of refractory epilepsy if we understood more clearly who is most likely to benefit.

In certain diseases, the KD is the definitive therapy. The KD is the treatment of choice for two disorders of energy metabolism, GLUT-1 deficiency and pyruvate dehydrogenase deficiency, the manifestations of which include medication-resistant epilepsy [47,48]. In these two disorders, the utilization of glucose as the primary energy molecule for the brain is impaired, and the ketogenic diet provides ketone bodies as an alternative fuel source, thereby ameliorating symptoms, including seizures.

Beyond these two metabolic disorders, evidence of increased KD effectiveness in specific epilepsy syndromes is only recently emerging. Multiple case series have suggested that the KD may be particularly useful in two early childhood myoclonic epilepsies: severe myoclonic epilepsy of infancy (SMEI, Dravet syndrome) and myoclonic–astatic epilepsy (MAE, Doose syndrome) [5,49–53]. We examined the treatment course of 23 children with myoclonic–astatic epilepsy followed at the Children's Hospital of Philadelphia [5]. Our definition of MAE included children with onset of myoclonic, astatic, or myoclonic–astatic seizures after 1 year of age who had normal development prior to onset of seizures and normal neurological exams and MRIs, and who did not have a predominance of tonic seizures or focal epileptiform discharges on the EEG. In our original cohort, 10 children were started on the KD after their seizures had failed to improve with an average of six other antiepileptic medications. Of these 10 children, 5 achieved seizure freedom and 1 experienced a substantial (>90%) drop in seizure frequency. Of the remaining 4 children, 3 were nonresponders and 1 stopped the KD after developing pancreatitis. The proportion of patients responding to the KD was substantially higher than the proportion responding to any other previous AED. Since the publication of this series, an additional 6 patients with MAE (5 boys, mean age at onset of afebrile seizures = 36 months) initiated KD treatment at our center. Of these, 5 became seizure free and 1 had a 50% or greater drop in seizure frequency (unpublished results). The small size of this retrospectively evaluated cohort precludes any strong statements about the comparative effectiveness of the KD in this population. However, our observation, along with the observations of others, suggests that use of the KD in children with MAE warrants further investigation.

The importance of understanding this relationship more clearly is twofold. First, it is conceivable that a diagnosis of MAE might be an indication for using the KD as a first-line treatment, sparing a child with this disorder exposure to ineffective medications with potential side effects. Because the diagnosis of MAE may be delayed until the appearance of characteristic seizure types, early KD initiation, in reality, may mean that it is used as the second or third antiepileptic medication. Nevertheless, successful KD use early in MAE may significantly reduce the morbidity that accompanies this disorder. Second, when we learn more about the underlying genetic determinants of MAE, we may gain further insights into the mechanisms of the KD. MAE may be a useful human model for understanding the pharmacodynamics of the KD.

Finding other markers that predict response to the KD in a broader population of children with medication-resistant epilepsy should be a research priority. To date, few factors have been identified that strongly predict KD response. Large observational studies of KD efficacy have not revealed differences between responders and nonresponders in age, sex, seizure type, epilepsy type, or EEG findings such as the presence of a normal background, focal abnormalities, or generalized epileptiform discharges [45,54,55]. There is tenuous evidence that KD failure is more likely in patients with partial seizures [56], discharges arising from the temporal lobe [57], or multifocal epileptiform abnormalities on the EEG [58].

We recently investigated whether EEG features present at baseline or early EEG changes after KD initiation predict KD response at 3 months [59]. The investigation was performed using a cohort of children previously enrolled in a randomized, controlled trial examining two different approaches to KD initiation [30]. Thirty-seven children with EEGs performed 1 week prior to KD initiation and at 1 and 3 months after KD initiation were included. KD response was defined as a 50% or greater improvement in seizure frequency assessed 3 months after KD initiation. The presence on baseline EEG of background slowing, qualitatively assessed and categorized as either moderate/severe or absent/mild, did not predict KD response. Similarly, on quantitative analysis, there were no differences between responders and nonresponders in mean relative power in delta, theta, alpha, or beta frequency ranges in the frontal, central, or posterior head regions. Improvement in background slowing between baseline, 1 month, and 3 months, qualitatively and quantitatively assessed, was seen in the majority of patients, but again, improvement did not predict responder status.

Spike index (SI), the percentage of seconds in the tracing containing epileptiform discharges, was evaluated during wakefulness. In responders, median SI declined from 9.4 (IQR = 1–43.3) at baseline to 1.2 (IQR = 0–10) at 1 month and 1.5 (IQR = 0–16) at 3 months, but these differences did not reach statistical significance ($P = 0.09$). Of the 14 patients who experienced a large drop in SI of 10% or more between baseline and 1 month, 12 were KD responders. Response to KD therapy was greater than six times more likely in those with improvement in SI of 10% or more at 1 month, than in those with no improvement or worsening of SI (unadjusted OR = 6.5, 95% CI = 0.85–75.4, $P = 0.03$).

Thus, although we were unable to determine any baseline EEG predictors of KD response, we did observe that patients with a drop in the burden of epileptiform discharges a month after KD initiation were far more likely to find success with the KD. The EEG should not replace and may not even augment the standard outcome measure of seizure reduction, but early improvement in the EEG may encourage families to continue the KD even if immediate seizure reduction is not seen. Additionally, EEG improvement in slowing and in epileptiform discharge frequency was observed in most patients, indicating that the KD may have broad neurophysiological effects, even in those who do not have a substantial reduction in seizures by 3 months.

The identification of additional neurophysiological and genetic markers associated with KD response may have implications for clinical care by encouraging targeted and earlier use of the KD. Also, markers predicting KD response may enhance our understanding of the mechanisms of action of the KD, which, in turn, may lead to development of related treatments. For example, changes in cortical excitability in healthy human adults as a result of short-term exposure to the KD have been demonstrated using paired pulse transcranial magnetic stimulation [60]. Specifically, increased activity of intracortical inhibitory circuits, which reflect primarily GABA-A receptor-mediated activity, was seen 2 weeks after KD initiation. These findings support the hypothesis that the KD enhances GABA transmission. Further investigation of this measure in subjects with epilepsy may provide insight into the connection between enhanced GABA action and the mechanism of action of the KD in reducing seizure frequency, particularly if there is a difference between KD responders and nonresponders either in baseline measures of cortical excitability or in the degree of change in intracortical inhibition after KD initiation. These are research questions that we are actively pursuing.

5. Summary

The ketogenic diet field continues to grow with dramatic changes in the understanding of both basic science underpinnings and clinical

science keys to success. As research continues to determine how best to provide dietary therapy and to whom, we suspect new insights will make the use of these nonpharmacological treatments more widely available, effective, and safer for both children and adults.

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