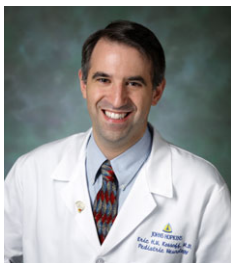


# Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group

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## SUMMARY



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Ketogenic dietary therapies (KDTs) are established, effective nonpharmacologic treatments for intractable childhood epilepsy. For many years KDTs were implemented differently throughout the world due to lack of consistent protocols. In 2009, an expert consensus guideline for the management of children on KDT was published, focusing on topics of patient selection, pre-KDT counseling and evaluation, diet choice and attributes, implementation, supplementation, follow-up, side events, and KDT discontinuation. It has been helpful in outlining a state-of-the-art protocol, standardizing KDT for multicenter clinical trials, and identifying areas of controversy and uncertainty for future research. Now one decade later, the organizers and authors of this guideline present a revised version with additional authors, in order to include recent research, especially regarding other dietary treatments, clarifying indications for use, side effects during initiation and ongoing use, value of supplements, and methods of KDT discontinuation. In addition, authors completed a survey of their institution's practices, which was compared to responses from the original consensus survey, to show trends in management over the last 10 years.

**KEY WORDS:** Ketogenic, Children, Epilepsy, Diet, Guideline.

Ketogenic dietary therapies (KDTs) are well-established, nonpharmacologic treatments used for children and adults with medication-refractory epilepsy. The classic ketogenic diet (KD) has been used continuously since 1921.<sup>1</sup> The parent-created support groups The Charlie Foundation (U.S.A.) in 1994 and then Matthew's Friends (UK) in 2004, have raised awareness and helped KDT centers succeed in patient recruitment and research. There are currently 4 major KDTs: the classic KD, the modified Atkins diet (MAD), the medium chain triglyceride diet (MCT), and the low glycemic index treatment (LGIT). There have been 4 randomized, controlled trials to date (3 with class III

evidence, and one with class II evidence) focusing on efficacy of KDT compared to continued medications or a placebo arm, which have led to recognition of KDTs as valid, scientifically based treatments.<sup>2–5</sup>

For many years, KDTs were started and implemented mostly based on anecdotal experience, individual institution (or country) practice, as well as chapters and books on the subject.<sup>6–8</sup> The classic KD was initiated historically in a hospital after a fast (over 2–3 days or until children became ketotic) followed by a gradual introduction of calories over a 3-day period. Children were then discharged and seen periodically in the clinic for medical and nutritional follow-

## KEY POINTS

- This manuscript represents a re-evaluation of ketogenic diet best practices, 10 years after the previous guideline publication
- Ketogenic diets should be used in children after 2 anti-seizure drugs have failed, and for several epilepsy syndromes perhaps even earlier
- There are 4 major ketogenic diets, and the one chosen should be individualized based on the family and child situation
- Flexibility in the initiation of ketogenic diets is appropriate, with fasting and inpatient initiation optional
- Children should be seen regularly by the ketogenic diet team, along with labs and side effect monitoring at each visit.

up. Laboratory monitoring, KD modification, and methods of discontinuation were handled primarily by dietitians with little scientific evidence to justify each center's approach.

The first attempt to publish a national consensus guideline occurred in Germany.<sup>9</sup> Recognition of the value of this document led to a desire to create a similar international guideline. As a result, The Charlie Foundation commissioned an international committee of neurologists and dietitians with expertise in KDTs in December 2006 at the American Epilepsy Society meeting in San Diego, California, U.S.A. The charge of this consensus group was to provide practical recommendations to guide management of KDTs. Published in 2009, this guideline has since proven very useful to the KDT community.<sup>10</sup> Now, nearly one decade later, the original organizers believed that enough new

research exists to update the consensus guideline, include more international experts, and document trends in management by comparing results from a current survey with the original survey of individual center management. Because basic science research into the mechanisms of action of KDT has also greatly increased over the past decade, additional translational information has been included in this updated version.

## METHODS

For the original consensus guideline, experts in the clinical use of the KDT were identified by both Beth Zupc-Kania, RD, CD, dietitian for the Charlie Foundation, and Eric Kossoff, MD, Medical Director of the Johns Hopkins Pediatric Ketogenic Diet Center. Identified clinicians had at least one first- or senior-authored, peer-reviewed publication regarding KDT or were a member of a center that had published about KDT. Attempts were made to avoid more than 3 clinicians from any one center. Twenty-six clinicians were identified for the original publication.<sup>10</sup>

This revised consensus was similarly organized by EK and BZK; all 26 previous authors were contacted to participate again. Drs. Per Amark and Eileen Vining declined due to recent retirements, Ms. Judy Nation is no longer in academics, and Dr. Heung-Dong Kim declined in favor of his colleague Dr. Hoon-Chul Kang. Including Dr. Kang, 9 additional authors with expertise and recent publications related to KDTs were asked and all agreed to participate. In total, this consensus now includes 31 authors, of which 6 (19%) are dietitians. Seventeen (55%) are from outside the United States.

Participants were asked to contribute a section either individually or in groups based on their individual expertise and

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an outline of clinical issues created by the 2 primary organizers (EK and BZK). Authors were instructed to cite peer-reviewed publications when available. In addition, for this version, Dr. James Wheless was assigned to review the document and assign levels of evidence based on the available scientific information (utilizing the American Academy of Neurology classification of evidence for therapeutic interventions). Unless mentioned, all evidence is Class IV. This information is included at the end of each section when applicable.

For the 2009 consensus guideline, a short survey of 15 questions was emailed to the 26 participants to obtain a group opinion. This process allowed us to share expertise when topics were controversial or where consensus was not clear. Results from this survey were then incorporated into the body of the manuscript, providing percentage responses for topics. We replicated this process for this revised manuscript, with some modifications to the previous questions for clarity, for a total of 20 questions. This consensus guideline has been reviewed and endorsed by the Child Neurology Society, Charlie Foundation, and Matthew's Friends.

## CONSENSUS RECOMMENDATIONS

### Patient selection

KDTs can effectively treat epilepsy in individuals from infancy through adulthood. For years it was thought that infants had difficulty maintaining ketosis while meeting their growth requirements. As a result, KDTs were not recommended for children younger than 2 years of age. A recent case report illustrates that KDTs are safe and effective for infants as young as 6 weeks.<sup>11</sup> In fact, there is now preliminary evidence that children younger than age 2 years may be an ideal age population in which to start the KD.<sup>12,13</sup> Specific guidelines for prescribing KDTs to infants have been created in Europe.<sup>14</sup>

Adolescents and adults had typically not been considered candidates for KDTs; only limited data for its benefit in these populations existed prior to the previous consensus statement.<sup>15–18</sup> Since then, however, there has been a large increase in interest and research suggesting similar outcomes in the use of dietary therapies for adults.<sup>19–22</sup> This topic is beyond the scope of this pediatric KDT consensus; however, it is extremely important to have an adult epilepsy diet center available when transitioning adolescent patients on KDT into adulthood.<sup>23</sup>

Traditionally, KDTs have been reserved as a “last treatment option” after establishment of medical intractability, typically defined as the failure of 2 or more antiseizure medications (ASDs). Given its efficacy, we strongly advocate that KDTs be considered earlier as an option for treatment of difficult-to-manage epilepsy.<sup>24,25</sup> When surveyed, the consensus group believed that KDTs should be offered to a child after a mean of 2.6 (standard deviation; SD 0.9) ASDs are tried unsuccessfully.

### Indications and contraindications

There are several specific conditions for which the group considered that KDTs should be used early in the course of epilepsy management (Table 1). These “indications” were classified as such as those in which at least 3 publications (from at least 2 KDT centers) consistently reported at least a 20% improvement in efficacy above the “norm” for KDTs (40–50% chance of at least a 50% seizure reduction), that is, conditions with 60–70% responder rates. For 7 specific conditions (glucose transporter 1 deficiency syndrome (Glut1DS), pyruvate dehydrogenase deficiency (PDHD), epilepsy with myoclonic-atic seizures, infantile spasms, tuberous sclerosis complex, children with gastrostomy tubes, and Dravet syndrome), 88% of the consensus group believed that KDTs should be strongly considered very early in the course of treatment.

As such, some conditions for which KDTs have been reported as helpful, but not clearly better than a 40–50% responder rate, were not classified for this revised guideline specifically as “indications.” In addition, reports of high efficacy from single centers or in one publication were not classified as indications for this revised consensus. An example of this is Lennox-Gastaut syndrome in which 51% of patients had >50% seizure reduction.<sup>26</sup> This condition and others are now listed in Table 2 as epilepsy conditions in which modest efficacy has been reported.

KDTs are the treatment of first choice for 2 distinct disorders of brain energy metabolism: Glut1DS and PDHD.<sup>27,28</sup> In Glut1DS, glucose transport across the blood-brain barrier is impaired, resulting in seizures (various types), often associated with developmental delay and a complex movement disorder.<sup>29</sup> In PDHD, pyruvate cannot be metabolized into acetyl-CoA, resulting in a mitochondrial disorder with lactic acidosis, seizures, and severe encephalopathy.<sup>29</sup> In both disorders, the concept of KDT is to provide ketones that bypass the metabolic defects and serve as an alternative cerebral fuel for the developing brain.

Introducing and maintaining KDTs for Glut1DS and PDHD does not differ from general recommendations as described in this consensus statement. Adverse effects do not differ from when KDTs are used more broadly in the treatment of intractable epilepsy and require similar monitoring in Glut1DS and PDHD. However, there are age-specific recommendations for the use of KDTs in Glut1DS. In infants and preschool children, the classic KD should be used primarily.<sup>14</sup> If effective and tolerated, the classic KD should be maintained as long as possible.<sup>30</sup> The MAD is used effectively in school-age children, adolescents, and adults with Glut1DS and provides a good alternative to the classic KD according to many families, especially in situations where the classic KD is proving difficult to tolerate long-term.<sup>31</sup> Adults with Glut1DS also benefit from KDT but may not tolerate the classic KD.<sup>32</sup> The LGIT is not recommended for treatment of Glut1DS or PDHD as it provides inadequate ketosis. The effect of triheptanoin, a new

**Table 1. Epilepsy syndromes and conditions (listed alphabetically) for which KDT has been consistently reported as more beneficial (>70%) than the average 50% KDT response (defined as >50% seizure reduction).**

|  |
|--|
| Angelman syndrome <sup>56,57</sup>   |
| Complex 1 mitochondrial disorders <sup>51,55</sup>                                       |
| Dravet syndrome <sup>35,36</sup>   |
| Epilepsy with myoclonic-atonic seizures (Doose syndrome) <sup>34,37,38</sup>             |
| Glucose transporter protein I (Glut-1) deficiency syndrome (Glut1DS) <sup>27,29-32</sup> |
| Febrile infection-related epilepsy syndrome (FIRES) <sup>44-47</sup>                     |
| Formula-fed (solely) children or infants <sup>48,49</sup>                                |
| Infantile spasms <sup>10,39,40</sup>   |
| Ohtahara syndrome <sup>50-52</sup>   |
| Pyruvate dehydrogenase deficiency (PDHD) <sup>28</sup>                                   |
| Super-refractory status epilepticus <sup>44,46,53,54</sup>                               |
| Tuberous sclerosis complex <sup>41-43</sup>  |

**Table 2. Several conditions (listed alphabetically) in which KDT has been reported as moderately beneficial (not better than the average dietary therapy response, or in limited single-center case reports)**

|  |
|--|
| Adenylosuccinate lyase deficiency <sup>64</sup>                                    |
| CDKL5 encephalopathy <sup>67</sup>   |
| Childhood absence epilepsy <sup>69</sup>   |
| Cortical malformations <sup>73,74</sup>  |
| Epilepsy of infancy with migrating focal seizures <sup>68</sup>                    |
| Epileptic encephalopathy with continuous spike-and-wave during sleep <sup>70</sup> |
| Glycogenosis type V <sup>65</sup>  |
| Juvenile myoclonic epilepsy <sup>66</sup>  |
| Lafora body disease <sup>58</sup>  |
| Landau-Kleffner syndrome <sup>61</sup>   |
| Lennox-Gastaut syndrome <sup>26</sup>  |
| Phosphofructokinase deficiency <sup>63</sup>                                       |
| Rett syndrome <sup>59,60</sup>   |
| Subacute sclerosing panencephalitis (SSPE) <sup>62</sup>                           |

compound composed of three, 7-carbon fatty acids, in Glut1DS has been encouraging in rodent studies and in pre-clinical trials but has yet to complete evaluation in ongoing human trials.<sup>33</sup> A majority of the consensus group (96%), however, believed that KDTs should be first-line for Glut1DS over triheptanoin, even in a patient without seizures (e.g. with a movement disorder).

In PDHD, the course of the disease is degenerative and monitoring the efficacy of KDTs often is difficult, especially in the absence of seizures to measure response. KDTs were effective and safe in one recent study of 19 children.<sup>28</sup> Data are based mainly on case reports. There are no publications on the use of MAD, MCT, or LGIT for the treatment of PDHD. The time and cost involved in KDT may be judiciously declined by some families of children with PDHD as life-extending, but not improving quality of life. Should this decision be made, the family's wishes should be accepted.

KDTs have also been described as particularly useful for certain epilepsy and genetic syndromes (Table 1). Myoclonic epilepsies, including Dravet syndrome and epilepsy with myoclonic-atonic seizures (Doose syndrome) appear to respond well to KDT.<sup>34-38</sup> The KD can be very beneficial in infants with West syndrome (infantile spasms), particularly those who are refractory to corticosteroids and vigabatrin.<sup>39,40</sup> There is evidence from 3 epilepsy centers for the benefits of KDT in tuberous sclerosis complex.<sup>41-43</sup> Additional indications include febrile infection-related epilepsy syndrome (FIRES),<sup>44-47</sup> formula-fed children,<sup>48,49</sup> Ohtahara syndrome,<sup>50-52</sup> super-refractory focal and myoclonic status epilepticus,<sup>44,46,53,54</sup> complex 1 mitochondrial disease,<sup>51,55</sup> and Angelman syndrome.<sup>56,57</sup> For FIRES and status epilepticus specifically, it is unknown if KDTs would have similar benefits when used earlier in the course of these conditions. Additional research is required as well for these conditions as most studies are single-center and retrospective, with possible selection bias.

Preliminary experience also showing some beneficial effects of the KD has been reported in epileptic encephalopathies such as Lafora body disease,<sup>58</sup> Rett syndrome,<sup>59,60</sup> Landau-Kleffner syndrome,<sup>61</sup> and subacute sclerosing panencephalitis (Table 2).<sup>62</sup> Single reports describe the use of the diet in metabolic disorders such as phosphofructokinase deficiency, adenylosuccinate lyase deficiency, and glycogenosis type V.<sup>63-65</sup> Other conditions with limited data include juvenile myoclonic epilepsy,<sup>66</sup> CDKL5 encephalopathy,<sup>67</sup> epilepsy of infancy with migrating focal seizures,<sup>68</sup> childhood absence epilepsy,<sup>69</sup> and epileptic encephalopathy with continuous spike-and-wave during sleep.<sup>70</sup>

All of the above strong and moderate indications have sufficient data in our guideline group's opinion to justify the use of KDT. However, are these reports enough to justify early or even first-line use? Many of these conditions have comorbid cognitive or behavioral abnormalities; would KDT ameliorate these issues as well? In addition, several of these indications have "preferred" ASDs (eg, valproate and clobazam for Dravet syndrome, corticosteroids and vigabatrin for infantile spasms). Does KDT work synergistically with these ASDs for these particular conditions? These important questions should be investigated in the years to come.

KDTs are contraindicated in several specific disorders (Table 3). The metabolic adaptation to KDT involves a shift from use of carbohydrates to lipids as the primary energy source. As such, a patient with a disorder of fat metabolism might develop a severe deterioration in the setting of fasting or KDTs. Therefore, before initiating the KDT, a child should be screened for disorders of fatty acid transport and oxidation if there is clinical concern for one of these conditions, especially in the setting of epilepsy without a clear etiology.



**Table 3. Contraindications to the use of KDT**

|  |
|--|
| <b>Absolute</b>  |
| Carnitine deficiency (primary)   |
| Carnitine palmitoyltransferase (CPT) I or II deficiency                    |
| Carnitine translocase deficiency   |
| $\beta$ -oxidation defects   |
| Medium-chain acyl dehydrogenase deficiency (MCAD)                          |
| Long-chain acyl dehydrogenase deficiency (LCAD)                            |
| Short-chain acyl dehydrogenase deficiency (SCAD)                           |
| Long-chain 3-hydroxyacyl-CoA deficiency                                    |
| Medium-chain 3-hydroxyacyl-CoA deficiency.                                 |
| Pyruvate carboxylase deficiency  |
| Porphyria  |
| <b>Relative</b>  |
| Inability to maintain adequate nutrition                                   |
| Surgical focus identified by neuroimaging and video-EEG monitoring         |
| Parent or caregiver noncompliance  |
| Propofol concurrent use (risk of propofol infusion syndrome may be higher) |

Long-chain fatty acids are transported across the mitochondrial membrane by carnitine, facilitated by carnitine palmitoyltransferase (CPT) I and II and carnitine translocase.<sup>71</sup> Once in the mitochondrion, fatty acids are  $\beta$ -oxidized to 2-carbon units of acetyl-CoA that can then enter the tricarboxylic acid cycle and be used for energy. An inborn metabolic error at any point along this pathway can lead to a devastating catabolic crisis (ie, coma, death) in a patient fasted or placed on KDT. Deficiency of pyruvate carboxylase is one example of this. KDTs are also contraindicated in porphyria, a disorder of heme biosynthesis in which there is deficient porphobilinogen deaminase. Propofol, a commonly used anesthetic that impairs mitochondrial function by uncoupling oxidative phosphorylation, can cause a rare but fatal syndrome of severe acidosis, rhabdomyolysis, and cardiac/hepatic/renal failure.<sup>72</sup> Children with mitochondrial disease may be at increased risk for propofol infusion syndrome when further challenged with KDTs.<sup>72</sup>

Although not a true contraindication, there is some evidence that children with epilepsy due to a focal lesion may do less well with KDT than with resective surgery.<sup>73</sup> In this situation, KDT may offer a period of both reduced seizures and ASDs, but not typically seizure freedom. In another study, better outcomes were demonstrated, with 10 of 21 (48%) with focal cortical dysplasia having prolonged periods of seizure freedom on the KD (compared to 59% of those in a comparison group receiving surgery).<sup>74</sup> The consensus group had a somewhat mixed opinion on whether to offer the KD for a child with a clear surgically resectable lesion, with 10 (40%) providing KDT in this situation, perhaps for a 3–6 month trial. Compared to the previous survey results, this is a lower percentile today (58% in 2009), perhaps due to improved lesion identification with advanced imaging, surgical techniques, and availability.

There are preliminary trials describing the potential benefits of KDTs for conditions other than epilepsy and the

metabolic conditions described previously. These include primarily autism spectrum disorder, Alzheimer disease, migraine, brain tumors, and traumatic brain injury.<sup>75</sup> At this time, there is growing but insufficient evidence to recommend the use of KDTs for these conditions other than on an investigational basis, although clinical trials are ongoing and are encouraged by the consensus group. In addition, a recent case series of 2 women with epilepsy treated with the KD and MAD during pregnancy showed safety; however, one infant had an ear deformity.<sup>76</sup> Further studies are required before the KDT during pregnancy can be recommended as safe and effective.

#### *Committee conclusions*

Ketogenic dietary therapies should be strongly considered in a child who has failed 2 antiseizure drugs. It is the treatment of choice for 2 specific disorders of brain metabolism, Glut1DS and PDHD. For Angelman syndrome, Dravet syndrome, FIRES, infantile spasms, epilepsy with myoclonic-atonic seizures, and tuberous sclerosis complex, KDT could be offered earlier. There was mixed opinion regarding use of dietary therapy in a child with a clearly approachable surgical lesion. Before starting KDT, one should consider inborn errors of metabolism that could lead to a severe metabolic crisis and ruled out if there is a clinical suspicion for these disorders.

#### **Pre-diet evaluation and counseling**

A clinic visit prior to initiation of KDT is strongly advised. The goals of this visit are to identify the seizure type(s), rule out metabolic disorders that are contraindications to KDT, and evaluate for complicating comorbidities (presence of kidney stones, swallowing difficulty, hypercholesterolemia, poor weight gain or oral intake, gastroesophageal reflux, constipation, cardiomyopathy, and chronic metabolic acidosis [Table 4]). Neurologists should review all current medications in partnership with a pharmacy and/or internet-based guides to determine carbohydrate content and options of switching to lower carbohydrate preparations while the patient is on KDT.

Before starting KDT, it is also crucial to discuss psychosocial issues influencing its implementation. The physician should ensure that caregivers understand their critical role in administering KDT to their child, including time involvement in meal preparation for the child who will require different meals than the rest of the family, costs of foods, avoidance of carbohydrates, additional supplementation, and potential side effects. One should also identify any behavioral or personality traits in the child or parent that will challenge successful administration of the diet and determine any food allergies and intolerances and cultural/religious preferences that will need to be considered in meal plans.

Screening laboratory studies should be obtained prior to starting KDT (Table 4). Renal ultrasounds are advised only

if there is a family history of kidney stones. A comprehensive evaluation should be undertaken if no clear etiology for the patient's epilepsy has been identified. Electroencephalography and brain magnetic resonance imaging (MRI) are essential to identifying those patients who are possible surgical candidates.

A key component of KDT is the information the family receives prior to the initiation of the diet. Helpful resources for families include publications, websites, and videos from support groups such as The Charlie Foundation and Matthew's Friends.<sup>6–8</sup> The majority of families wishing to initiate the KD obtain information about it from their neurologist; however, more than half also obtained information about the KD from websites.<sup>77</sup> High glycemic carbohydrate foods can be reduced, small amounts of fat-rich foods can be trialed, and possibly increasing fluid intake (if low) can be suggested in advance of KDT.

Parental expectation should be discussed in advance; not only seizure reduction, but also possible medication reduction and cognitive improvement.<sup>78</sup> The team should keep the expectations realistic for each family and child. The expected length of time on KDT should be discussed. A minimum of 3.2 months (SD 1.3) to allow for potential improvement to occur is advised.

Short-term difficulties are not uncommon at the time of KDT initiation and should be discussed with families; those occurring during the first week of the KD do not portend poor efficacy later.<sup>79</sup> A social worker or nurse on the team can be instrumental in helping the family transition to KDT by assessing family needs, financial limitations, and gathering resources, and contacting other families on KDT for parent-to-parent support.

Parents should consider bringing games, books, and favorite feeding utensils to help keep the child comfortable during this time. Topics including the KD prescription, meal planning, preparation, cooking, use of the gram scale, managing sick days, traveling, celebrations, nutritional status, and supplements should be discussed during the KDT education program. Child life specialists can be helpful here by contacting the family in advance of the admission to discuss ways to make the hospitalization more comfortable.<sup>80</sup>

#### *Committee conclusions*

There are several important prerequisites to starting dietary therapy to ensure safety and to maximize the chance of success (Table 4). Dietary therapy should be provided for at least 3 months before considering the therapy nonefficacious and discontinuing KDT.

#### **Specific diet selection and provision**

There are 4 major KDTs with published evidence supporting their use. The first 2 created, the classic long-chain triglyceride (LCT) KD and the medium-chain triglyceride (MCT) diet, have been in existence the longest and are typically started in the hospital by a dietitian and neurologist.

The LCT diet has been the more traditional KD treatment, for which most data are available, and is used by every center in this consensus group. The MCT diet may be preferable in some cases.<sup>81–84</sup> In the classic KD, the fat source is predominantly LCT, which is obtained primarily from standard foods. MCT oils yield more ketones per kilocalorie of energy than LCTs. This increased ketogenic potential means less total fat is needed in the MCT diet, thus allowing the inclusion of more carbohydrate and protein and potentially food choices. There is no evidence for different efficacy between the MCT and classic KD (Class III evidence).<sup>82,83</sup>

The classic KD is calculated in a ratio of grams of fat to grams of protein plus carbohydrate combined. The most common ratio is 4 g of fat to 1 g of protein plus carbohydrate (described as “4:1”); 90% of calories are from fat. A 3:1 or lower ratio can be used alternatively to increase protein or carbohydrate intake; this is more appropriate as well for diet initiation in infants. There is one publication reporting that a 4:1 ratio, when used at initiation, may be more advantageous for the first 3 months in older children, after which the ratio can be reduced.<sup>85</sup>

Calories have traditionally been restricted to 80–90% of the daily recommendations for age; however, this has never been shown in patients to be beneficial and most centers do not routinely calorie restrict.<sup>86,87</sup> A 3-day food record can be obtained prior to KDT initiation and used to estimate current and future caloric needs. Historically, patients on KDT have been fluid restricted to 90%, a practice that was not based on scientific evidence. Most centers no longer fluid restrict children on KDT.

The traditional MCT diet is used by 10 (40%) of the consensus ketogenic diet centers and comprises 60% energy from MCT. This level of MCT can cause gastrointestinal discomfort in some children. To improve this difficulty, a modified MCT diet was created, using 30% energy from MCT oil, with an additional 30% energy from long chain fats.<sup>82</sup> Many children will be on a 40–50% energy MCT diet, and can tolerate as high as 60% if necessary. MCT oil has also been used as a supplement to the classic KD to boost ketosis, improve lipid abnormalities, and due to laxative properties. MCT can be given in the diet as coconut oil or as an emulsion. MCT should be included in all meals when used. Better toleration may be achieved using less MCT with each meal but providing more meals per day. MCT oil consumption may also cause throat irritation due to the presence of C6 (caproic acid).<sup>88</sup>

The KD may be provided as an all-liquid, formula-based diet.<sup>48,49</sup> Liquid diets may be appropriate for both infants and enterally fed children via gastrostomy and jejunostomy tubes. An additional benefit to enteral delivery is very high compliance rates, and efficacy is also high, hence the inclusion of this situation as an indication in Table 1.<sup>48,49</sup> To prepare a formula-based KD, there are a variety of commercial products available. All products are fortified with vitamins

**Table 4. Recommendations for pre-KDT evaluation**

|   |
|---|
| <b>Counseling</b>   |
| Discuss seizure reduction, medication, and cognitive expectations                                       |
| Potential psychosocial and financial barriers to the use of KDT   |
| Review anticonvulsants and other medications for carbohydrate content                                   |
| Recommend family read parent-oriented KDT information   |
| Child life specialist contact in advance of admission, if available                                     |
| <b>Nutritional evaluation</b>   |
| Baseline weight, height, and ideal weight for stature   |
| Head circumference in infants   |
| Body mass index (BMI) when appropriate  |
| Nutrition intake history: 3-day food record, food preferences, allergies, aversions, and intolerances   |
| Establish diet formulation: infant, oral, enteral or a combination                                      |
| Decision on which diet to begin (classic KD, MCT, MAD, and LGIT)  |
| Calculation of calories, fluid, and ketogenic ratio (or percentage of MCT oil or carbohydrates per day) |
| Establish vitamin and mineral supplementation based on dietary reference intake                         |
| <b>Laboratory evaluation</b>  |
| Complete blood count with platelets   |
| Electrolytes to include serum bicarbonate, total protein, calcium                                       |
| Serum liver and kidney tests (including albumin, blood urea nitrogen, creatinine)                       |
| Fasting lipid profile   |
| Serum acylcarnitine profile   |
| Vitamin D level   |
| Urinalysis  |
| Antiseizure drug levels (if applicable)   |
| Ancillary testing (optional)  |
| EEG   |
| MRI of brain  |
| ECG (echocardiogram), strongly consider if history of heart disease                                     |
| Urine organic acids (if diagnosis unclear)  |
| Serum amino acids (if diagnosis unclear)  |

and minerals; however, age-appropriate requirements should be considered, and diets should be supplemented to meet the Dietary Reference Intakes (DRIs) established by the National Academy of Sciences. In addition, breastfeeding is possible by either calculating the amount of breastmilk into a 3:1 formula or potentially allowing it briefly on demand.<sup>11,14</sup>

The KD may also be delivered as a blenderized formula created from pureed foods, although there are no published clinical trials regarding its use at this time. The blenderized formula should be prepared with a high-quality blender to prevent blockage of the feeding tube, with the addition of a liquid fat source, diluted with water, and supplemented with micronutrients. This formula may be helpful when allergies to both soy and milk protein are present or when parents wish to use organic foods for their tube-fed child. The Charlie Foundation has published a guide on preparing blenderized formulas for enteral use ([www.charliefoundation.org](http://www.charliefoundation.org)).

In the past 16 years, 2 other dietary therapies have been developed for the treatment of epilepsy: the Modified Atkins Diet (MAD) and Low Glycemic Index Treatment (LGIT).<sup>24,25,89,90</sup> Both of these KDTs are initiated

universally as outpatients and they do not require precise weighing of food ingredients. They tend to require less dietitian time for meal calculations and allow more parental independence. The MAD is offered by 23 (92%) of consensus ketogenic centers and the LGIT by 17 (68%).

The MAD is a high-fat, low-carbohydrate therapy similar to the classic KD in food choices, and typically provides approximately a 1:1–1.5:1 ketogenic ratio, but no set ratio is mandated and some children can achieve as high as a 4:1 ratio.<sup>24</sup> The initial daily carbohydrate consumption on the MAD is approximately 10–15 g (comparable to the strict initiation phase of the Atkins diet used for weight loss), with a possible increase to 20 g per day after 1–3 months.<sup>90</sup> However, there is no limitation on protein, fluids, or calories, making meal planning easier. In addition, as detailed calculations are not required, this diet may be ideal for low-resource settings with a paucity of trained dietitians.

The MAD has been shown to be effective in children with refractory epilepsy in a randomized controlled trial (Class III evidence).<sup>4</sup> A further simplified version of the MAD using household measures and photographs was useful for parents with low levels of literacy in a randomized controlled trial in India.<sup>91</sup> The MAD was as effective as the classic KD in children with refractory epilepsy in a randomized study; however, children <2 years of age had a higher chance of seizure freedom with the classic KD (Class III evidence).<sup>13</sup> Although, 2 small uncontrolled studies suggest that the MAD is effective in young children,<sup>92,93</sup> the majority of the consensus group (92%) at this time offers only the classic KD (not the MAD) to children <2 years of age. For adolescents and adults, the MAD or LGIT is preferred by most (72%) of the consensus group largely due to better adherence.

The LGIT was designed based on the hypothesis that stable glucose levels play a role in the mechanism of the KD.<sup>25</sup> The LGIT allows liberalization of total daily carbohydrate intake to approximately 40–60 g/day, but favors carbohydrates with low glycemic indices <50. A few uncontrolled studies suggest that the LGIT may be efficacious in children with refractory epilepsy, but there are no trials comparing the LGIT with other KDTs.<sup>94–97</sup> The LGIT has been reported as particularly effective in children with Angelman syndrome, including a single center case series of 23 patients.<sup>56</sup>

#### Committee conclusions

The specific KDT chosen should be individualized based on the family and child situation, rather than perceived efficacy, together with the expertise of the KDT center. Calorie and fluid restriction are no longer recommended. Children younger than 2 years of age should be started on the classic KD (Class III evidence), and a formula-based KD may be helpful for this age group. There is reasonable evidence for the use of the MCT (Class III), MAD (Class III), and LGIT, and most consensus ketogenic centers are offering these

options for KDT. These latter 2 therapies are recommended for adolescents, but centers may choose the classic KD for individual cases, especially in those with enteral feeding. The MAD is being studied for use in areas with limited resources.

### Initiation of dietary therapies

Most (20/25, 80%) centers begin the classic KD in the hospital so that the child can be observed closely, and medical interventions can be instituted if needed. The hospital admission also provides more time for teaching of caretakers on how to calculate and weigh foods, monitor ketosis, and manage the KD once the patient leaves the hospital. It is not clear how frequently inpatient initiation unmasks rare metabolic disorders, since the advent of preadmission metabolic testing.

The KD can alternatively be started as an outpatient, based on several retrospective studies in which no fasting period was used.<sup>86,98,99</sup> The potential advantages of this include reduced family stress, time away from home, and hospital-associated costs. Although, as stated previously, most centers still routinely admit for KD initiation, 23/25 (92%) believed that an outpatient initiation could be used in select situations. This percentage was higher than the 2009 consensus survey (73%). To initiate the classic KD as an outpatient, all children must be screened with metabolic testing, the child must be in proximity to medical care, and the KD team must be able to provide family education in an outpatient setting. A recent European consensus-based guideline recommends hospitalizing infants (<12 months) for initiation of the classic KD, using a nonfasting protocol.<sup>14</sup>

The traditional method of initiating the KD involves a period of fasting (12–24 h), with no carbohydrate-containing fluids provided. For the first 24–48 h, serum glucose is monitored periodically (eg, before meals) and juice or other forms of dextrose are provided for values <30 mg/dl. The meals are then typically advanced daily to by one-third or one-half caloric intervals until full calorie meals are tolerated, while keeping the KD ratio constant. A different approach begins with full calories, but the KD ratio increases daily from 1:1, 2:1, 3:1, to 4:1 to allow the child to acclimate to the increasing concentration of fat.<sup>100</sup> Evidence also exists that the KD can be started at full calories at a ratio of 4:1 on day 1, with no prolongation of hospital stay, increased adverse effects, or decreased efficacy at 3 months.<sup>87</sup> All of these approaches are valid and at the KD center's discretion.

Neither ketosis nor seizure control at 3 months is improved with a fast at KD initiation.<sup>100,101</sup> In addition, weight loss, hypoglycemia, and acidosis were less common when children were not fasted.<sup>100</sup> Fasting may lead to a quicker onset of seizure reduction, and therefore may be advantageous when a more immediate response is desired, such as in refractory status epilepticus.<sup>102,103</sup> Similar to the

2009 consensus survey, 17/25 (68%) believed that fasting was optional but at times had a role in the start of the KD (58% in 2009), often in situations in which a more rapid KDT benefit was desired (eg, status epilepticus). However, no center believed it was mandatory (vs 11% in 2009). Of note, despite this “optional” recommendation, 18/25 (72%) do not routinely fast children at their ketogenic centers, with the remainder (28%) individualizing on a case-by-case basis, reflecting a change in current practice. No center believed it was appropriate to fast a child younger than age 2 years.

In 1996, The Charlie Foundation produced the program “KetoDietCalculator” to assist professionals and caregivers in managing dietary therapies. This online database calculates meal plans for all ages, from infants to adults, from solid food to liquid formulas, and, is available on the internet and on mobile devices ([www.ketodietcalculator.org](http://www.ketodietcalculator.org)). This program is designed for the classic KD and MCT, which require a gram scale to weigh meals versus the LGIT and MAD therapies that are less precise and therefore less labor intensive. The ketodietcalculator requires a licensed nutritionist to set up an individualized diet calculation before providing access to the family. The program receives daily updates and is housed on a secured server. Another program in existence is EKM (Electronic Ketogenic Manager) available for free for patients and families from the Matthew's Friends charity. This program is updated regularly and includes foods from United Kingdom but is available worldwide.

Most centers initiate the MAD and LGIT in the outpatient setting, often using group teaching sessions, and without a fasting period. In these cases, the main aim is the opportunity for teaching of the caregivers on how to manage the MAD or LGIT at home. In the MAD, fat intake (eg, cream, butter, oils, ghee) is actively encouraged. Protein intake is not restricted, but if very high may interfere with ketosis. There is no calorie restriction with the MAD. The LGIT is individualized for calories, grams of protein, fat, and carbohydrate (protein contributes 20–30% of calories, while fat contributes 60%). With the LGIT, carbohydrate intake is limited to 40–60 g/day and restricted to carbohydrate-containing foods with a glycemic index <50. MAD education includes carbohydrate counting, reading food labels, and identifying and encouraging high fat foods. LGIT education also includes background on the concepts of the glycemic index.

### Committee conclusions

Flexibility in the initiation of KDT is well-supported based on clinical studies. Fasting should be considered optional, recognizing that the majority of this consensus group no longer prescribes fasting at KDT onset. Fasting may be appropriate when a quicker time to response is desired but is not necessary for long-term efficacy and has more immediate side effects. The KD can be started in



outpatients, although most centers still routinely admit for initiation. The MAD and LGIT are typically started in outpatients and without a fasting period.

### Concurrent antiseizure drugs

KDT are used in children whose seizures have failed to respond to ASDs and are usually used in combination with these drugs. At present, data are sparse supporting significant pharmacodynamic interactions between ASDs and the KD in humans. One study found that children on the KD with concomitant use of lamotrigine had decreased efficacy and lower ketones than children not on lamotrigine.<sup>104</sup> Animal studies showed that acetone enhanced the anticonvulsant activity of some commonly used ASDs: valproic acid, carbamazepine, lamotrigine, and phenobarbital.<sup>105</sup> In this study, the brain concentrations of ASDs were not affected and the authors hypothesize that it might be a pharmacodynamic interaction. KDT may have synergistic benefits when used in combination with a nonpharmacological therapy, namely vagus nerve stimulation.<sup>106</sup>

Studies on pharmacokinetics of ASDs during KDT have found that serum levels of most commonly used ASDs do not appear to be significantly altered.<sup>107–109</sup> Thus, as a rule, dose adjustments of concomitant ASDs at KDT start are not needed. In case of increased side effects or lethargy, plasma levels should be checked and ASDs that cause sedation such as benzodiazepines and phenobarbital should be reduced.

Valproic acid, an ASD often used for refractory generalized epilepsies for which KDT is proposed, has a historical concern when used in combination. This may be because valproic acid, as a short-chain fatty acid itself, could increase fatty acid oxidation and perhaps resultant hepatotoxicity. Despite this concern, clinical data generally support the safe use of valproic acid with KDT.<sup>110,111</sup> In a case of hepatotoxicity while a patient was receiving the KD and valproic acid, it was shown that after tapering both, the KD could be tried successfully later.<sup>112</sup> In rare cases, valproic acid during KD inhibits ketosis and when removed, increased ketosis and clinical symptoms appeared.<sup>111</sup> Secondary carnitine deficiency, which can occur with either KDT or valproic acid alone, can be worsened and should be monitored.<sup>113</sup>

KDTs are also known to cause a chronic but often mild or clinically asymptomatic metabolic acidosis. Adding KDT to an existing regimen of carbonic anhydrase inhibitors (acetazolamide, topiramate, zonisamide) may worsen preexisting metabolic acidosis, but the greatest decreases in serum bicarbonate levels occur early after initiation of KDT.<sup>114</sup> It is recommended that bicarbonate levels should be monitored carefully when patients are receiving these ASDs. It does not appear that topiramate, which can increase the risk of kidney stones separately, raises the incidence when used in combination with KDT, but there may be increased risk with zonisamide.<sup>115,116</sup> It is prudent to observe children for stones more carefully when they are given carbonic

anhydrase inhibitors and it may be less of an issue if oral citrates are used empirically.<sup>117</sup>

Discontinuing ASDs is often one of the parent or patient goals of KDT, and it is typically advised after the first month of KDT use. However, there is evidence that ASDs can be reduced successfully even during the first month of the classic KD.<sup>118</sup> Phenobarbital and benzodiazepine reductions may be associated with a higher risk of seizure worsening on KDT; therefore, it is recommended that they should be tapered gradually.<sup>118</sup> Children do not need to be seizure-free on KDT in order to attempt reduction of concurrent ASDs.

Finally, ingestion of carbohydrates may quickly reverse the ketosis achieved by KDT in some children, and lead to resumption in seizure activity.<sup>81</sup> Clinicians should be mindful that formulations of many drugs, including medications not for seizure control, may contain carbohydrates or sugars as additives. Prescribers should seek alternative formulations whenever possible or include the amount of carbohydrate into KDT calculations.<sup>119</sup> In general, tablets are preferred over liquid or chewable medications.

### Committee conclusions

There is little evidence of any consistent beneficial interactions between KDT and ASDs. Conversely, there are no particular ASDs that are to be avoided with KDT. ASDs may be reduced after 1 month if KDT is successful, although caution is advised when reducing phenobarbital or benzodiazepines.

### Supplementation

Due to the limited quantities of fruits, vegetables, enriched grains, and foods containing calcium in KDT, supplementation is essential, especially for B vitamins (Table 5). Carbohydrate-free multivitamin and mineral products should be used. There is insufficient vitamin D and calcium in KDT food and coupled with the evidence for decreased vitamin D levels in children with epilepsy, that leads to the suggestion that both vitamin D and calcium should be provided at the recommended daily allowance.<sup>120,121</sup> Only half (52%) of the consensus group provides additional vitamin D beyond the RDA guidelines.

In the previous consensus guideline, there was little evidence regarding additional supplementation (eg, zinc, selenium, magnesium, phosphorus). In 2011, there was a systematic review of vitamin A, E, zinc, selenium, and magnesium levels of 91 children on both the classic KD and MCT diet.<sup>122</sup> Vitamin A and E remained high in both groups, but selenium and magnesium levels dropped at 12 months on the diet in the classic KD group. A more recent study also found that serum selenium levels drop after 6 and 12 months on KDT,<sup>123</sup> and 3 studies have identified a link with cardiomyopathy.<sup>124–126</sup> However, it is still unclear if additional selenium beyond what is provided in a standard multivitamin is required, but it appears to be

important to periodically check levels. Only 11 (44%) of the consensus group routinely provides additional selenium.

There is no current evidence for any other vitamins, probiotics, or omega-3 fatty acids in combination with KDT at this time. Although exogenous ketone supplements are becoming widely commercially available, and ketone esters are under active investigation, there is no evidence for their role in the treatment of epilepsy or as supplementation for children receiving KDT currently. Finally, ketogenic pre-made products (eg, baking mixes, pizza, rolls, milkshakes) are available and several are marketed for use by patients on KDT. These appear safe to use, may improve compliance and tolerability while maintaining ketosis, but are not required for those on KDT.

There is Class III evidence for the preventative use of oral citrates (Polycitra K specifically studied) to reduce the risk of kidney stones. In a retrospective study, the risk was reduced 3-fold with their use, initiated solely with abnormal urine calcium to creatinine results.<sup>127</sup> This led to a study evaluating the empiric use of oral citrates for all children starting the classic KD, which led to a reduction in incidence from 6.7% to 0.9%, without adverse effects.<sup>117</sup> Citrates may also reduce acidosis and theoretically bone mineral loss; however, their folic acid absorption could be theoretically negatively affected as well, causing higher risk of megaloblastic anemia.<sup>128</sup> Fourteen (or 56%) of the consensus group routinely use empiric oral citrates for all children. Because the study evaluating the use of empiric oral citrates was published since the last consensus statement, this survey question regarding usage was not asked in 2009.

Gastrointestinal dysmotility is a common side effect of KDT; however, empiric supplementation to alleviate this has not been studied.<sup>129</sup> Children are often started on H<sub>2</sub>-blockers or proton pump inhibitors for gastroesophageal reflux, but most commonly after this condition occurs. Constipation is even more common on the classic KD (not MCT), and parents should be aware of prevention techniques including the use of higher fiber vegetables, sufficient fluids and, if necessary, the use of carbohydrate-free laxatives such as Miralax™.

Carnitine supplementation has been a controversial issue for many years. Since the previous consensus statement, there have been no new data supporting or refuting its use. Secondary hypocarnitinemia may rarely cause liver and heart problems.<sup>130</sup> Symptoms indicating hypocarnitinemia may include fatigue and muscle weakness. Prolonged use of ASDs such as valproate, poor nutritional status, and long-term use of KDT can cause secondary hypocarnitinemia, especially in younger patients.<sup>113</sup> When surveyed, 22 (88%) of consensus centers check carnitine levels while on dietary therapy. Carnitine supplementation may also be expensive if not covered by insurance and adds an additional medication that is often dosed 3 times a day. The majority of ketogenic centers (84%) recommend that carnitine should be supplemented orally only if levels are low

or children become symptomatic, which is similar to the 2009 consensus (92%). Only 4 centers (16%) empirically start children on carnitine.

#### *Committee conclusions*

All children should receive a daily multivitamin and calcium with adequate vitamin D. Oral citrates appear to prevent kidney stones (Class III); however, there was a mixed opinion on empiric use. Vitamin D levels decrease on the KD, but again, there were split opinions on empiric extra supplementation. There is no recommendation for the empiric use of antacids, laxatives, probiotics, exogenous ketones, additional selenium, or carnitine with the KD at this time.

#### **Maintenance of children receiving dietary therapies**

The child on KDT should be seen regularly for follow-up evaluation by both dietitians and neurologists familiar with KDT (Table 6).<sup>131,132</sup> Phone or email contact within the first month is advised; the child should be seen in clinic after 1 month as well to ensure that the KDT is being implemented correctly and to provide in-person early support. Ninety-two percent of the group believed that the child should be seen at 1 month on KDT, which is a new recommendation from the consensus group. Afterward, children should be seen at 3, 6, 9, and then 12 months, with frequent email or phone contact in-between. A child younger than 1 year of age should have even more frequent contact with the KDT team.<sup>14</sup> Adjustments in KDT or ASDs are typically done in most children on KDT, to reduce side effects and improve seizure control.<sup>133</sup> Those with a lower baseline seizure frequency and younger age of seizure onset were more likely to see additional benefit by fine-tuning modifications.<sup>133</sup> After 1 year on KDT, visits can be spaced out to every 6 months with phone or email contact in the interim.

Urine ketones should be checked at home by parents several times per week, preferably at different times of the day, as urine ketones can be low in the morning and higher in the evening. There are data regarding the value of serum BOH (beta-hydroxybutyrate), with some studies suggesting that serum BOH may better correlate with seizure control.<sup>134–136</sup> Serum ketosis is more accurate, but more expensive and requires finger sticks. The current guideline for infants on the KD recommends serum BOH monitoring.<sup>14</sup> Several members of the consensus group suggested that obtaining serum BOH at routine KDT clinic visits was valuable, especially during the diet-initiation period, and 44% (11/25) of the group have parents use home BOH meters. This was higher than the previous consensus statement (15% recommending home BOH meters). BOH monitoring may be reasonable when urine ketones results do not clinically match seizure control or fluctuate without explanation.

In addition to a complete examination with accurate weight and height measurement at each follow-up visit, laboratory studies are recommended (Table 6). These labs

**Table 5. Supplementation recommended for children receiving KDT**

|  |
|--|
| <p>Universal recommendations</p> <p>Multivitamin with minerals (including trace minerals, especially selenium)</p> <p>Calcium and vitamin D (meeting daily RDA requirements)</p> <p>Optional extra supplementation</p> <p>Vitamin D (above RDA)</p> <p>Oral citrates (eg, CitraK or PolycitraK)</p> <p>Laxatives: Miralax, mineral oil, glycerin suppository</p> <p>Additional selenium, magnesium, zinc, phosphorus, iron, copper</p> <p>Carnitine</p> <p>MCT oil or coconut oil (source of MCT)</p> <p>Salt (sodium to add to RCF formula if used for greater than age 1 year)</p> |
| <p>All supplements listed should be provided as carbohydrate-free preparations whenever possible.</p>  |

should include at least a complete blood count with platelets, liver and renal profiles, fasting lipid values, calcium, vitamin D, and magnesium and should be obtained every 3 months while the patient is on a KDT during the first year, but then potentially less often (eg, every 6–12 months) afterward. Fasting cholesterol and triglyceride levels typically rise short-term and should be monitored, recognizing that they often return to baseline after 9–12 months.<sup>137</sup> Most centers also check serum carnitine profiles (free and total), selenium levels, urine calcium and creatinine values, and blood anticonvulsant levels. Less frequently, centers will check routine renal ultrasounds (10/25, 40%), electrocardiography (ECG) (10/25, 40%), and carotid ultrasounds (2/25, 8%).

Children with treatment-resistant epilepsy are at high risk for poor bone health due to prolonged ASD exposure, direct and indirect effects of ASDs on calcium and vitamin D metabolism, and comorbid conditions such as cerebral palsy that affect weight-bearing. The combined effect of KDT creating a high “acid load” via the ketone bodies, alterations in vitamin D, and lowering of growth factors contributes to increasing this risk.<sup>121,138,139</sup> Approximately half (12/25, 48%) of centers advocate screening with dual energy X-ray absorptiometry (DEXA) scans in children to evaluate for osteopenia, in those on the KD for over 2 years. If obtained, abnormal results should lead to possible interventions and repeat scans in 1 year.

There is no requirement to obtain regular EEG studies for patients while on dietary therapy. EEG may be used as a predictor of response to KDT when performed early, with a reduction in the interictal epileptiform discharges correlating with seizure response at 3 months.<sup>140</sup> EEG can also be used when deciding to withdraw ASDs or even KDT after some time. Sixty-four percent (16/25) of centers check a routine EEG prior to KDT discontinuation, which is nearly double the 2009 consensus (35%).

Ongoing nutritional care during KDT is necessary to ensure nutritional adequacy, support compliance, and to

advise on individualized supplementation and fluid intake. Ensuring nutritional adequacy includes prescribing appropriate calories, but also meeting guidelines for vitamins, minerals, essential amino and fatty acids, and water. If a child is overly hungry or is not eating sufficiently, calories should be adjusted accordingly. There is no evidence that excessive weight gain or loss adversely affects KD effectiveness for seizure control.<sup>141</sup>

Nutritional ketosis can be adjusted through diet manipulation to try to improve seizure control. Increasing the fat content of the diet and lowering the carbohydrate and/or protein is a method that can be trialled to induce deeper ketosis. This is known as “increasing the ratio” in classic KD terminology. Similarly, lowering the fat content can reduce ketosis which may be desirable when ketosis is too strong (ie, causing lethargy) or if weaning KDT. Ketogenic practitioners have occasionally incorporated MCT oil into the classic KD to achieve higher ketosis while maintaining the same ratio and for its added benefit as a laxative effect and easier digestibility over long-chain fats.

With regard to selecting the optimal ratio when using the classic KD, a single study evaluating a planned decrease from a 4:1 to 3:1 ratio after 3 months determined that seizures did not worsen when this change was made.<sup>85</sup> Ratios higher than 4.5:1 are generally not used for more than a few months due to the increased risk of adverse effects, limited protein, and poor compliance. An exception is the use of KDT for status epilepticus (via a feeding tube) where higher ratios have been trialed to augment maximum ketosis over a short period of time (ie, up to 2 weeks). In one study, fine-tuning KDT adjustments (eg, ratio increases, calorie changes, and supplementation) led to additional seizure control in 18% of children.<sup>133</sup> Lowering the KDT ratio may improve compliance when indicated.

Low carbohydrate diets have a diuretic effect. In addition, unlike a normal diet, the contribution of fluid from the restricted volume of food in KDT is minimal. Liberalization of fluid should be considered for patients at increased risk for dehydration. It is helpful for families to be counseled on appropriate fluid volume as a daily goal. A urine specific gravity within normal limits (<1.020) is a measure of adequate hydration that may be used by caregivers at home if needed.

#### *Committee conclusions*

Children should be seen at 1, 3, 6, 9, and 12 months on KDT in the first year, with visits spaced to every 6 months after that. More frequent contact is necessary for infants and other patients at high risk for nutritional deficiency. All children should be seen by a pediatric neurologist and dietitian at clinic visits. At each visit, nutrition, labs, ASD use, and KDT duration should be discussed. Prior to KDT discontinuation, an EEG should be considered.

**Table 6. Recommendations for aspects of a follow-up KDT clinic visit**

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|--|
| <p>Nutritional assessment (registered dietitian)<br/> Height, weight, ideal weight for stature, growth velocity, BMI when appropriate<br/> Head circumference in infants<br/> Review appropriateness of KDT prescription (calories, protein, and fluid)<br/> Review vitamin and mineral supplementation<br/> Assess compliance to KDT<br/> Adjust KDT if necessary to improve compliance and seizure control</p> <p>Medical evaluation (neurologist)<br/> Efficacy of the diet (is the KDT meeting parental expectations?)<br/> Side effects of KDT<br/> Antiseizure drug reduction (if applicable)<br/> Should KDT be continued?</p> <p>Laboratory assessment<br/> Complete blood count with platelets<br/> Electrolytes to include serum bicarbonate, total protein, calcium<br/> Serum liver and kidney profile (including albumin, blood urea nitrogen, creatinine)<br/> Vitamin D level<br/> Fasting lipid profile<br/> Free and total carnitine<br/> Urinalysis<br/> Selenium level<br/> Anticonvulsant drug levels (if applicable)<br/> EEG (at KDT discontinuation consideration)</p> <p>Optional<br/> Serum beta-hydroxybutyrate (BOH) level<br/> Urine calcium and creatinine<br/> Zinc, copper levels<br/> Renal ultrasound<br/> ECG<br/> Bone mineral density (DEXA scan) after 2 years on the KD</p> <p>Visits should be at least every 3 months for the first year of KDT, with a visit 1 month after starting KDT also advised.</p> |
|--|

### Adverse effects

Side effects of KDT occur, and neurologists and dietitians need to understand how to manage them.<sup>129,142,143</sup> The most common involve the gastrointestinal system and are often seen during the initial few weeks of dietary therapy. Constipation, emesis, and abdominal pain may occur in up to 50% of children.<sup>79,129,144</sup> These symptoms are usually mild and easy to correct with minimal interventions. When adequately managed and prevented, gastrointestinal side effects are rarely a reason to discontinue KDT.

Hyperlipidemia is a well-known side effect of almost all KDT.<sup>137,145–148</sup> Increased serum triglycerides and total and low-density lipoprotein (LDL) cholesterol levels have been reported in 14–59% of children on the classic KD.<sup>129,137,147,148</sup> Hyperlipidemia can be seen as early as the first month of therapy.<sup>148</sup> Preliminary data suggest that despite an early increase in serum lipids during the first months of KDT, this increase is usually temporary. In one study, 60% of those on the classic KD had hypercholesterolemia (>200 mg/dl).<sup>147</sup> By 12 months, the serum lipid

values often normalize and remain within normal limits.<sup>137,149</sup>

Most centers are reluctant to start KDT in children with preexisting hyperlipidemia. However, in one study, it was shown that despite the high dietary fat content of KD, serum levels can be controlled in children with hyperlipidemia prior to starting the classic KD.<sup>146</sup> Strategies to prevent KD-induced hyperlipidemia include increasing consumption of MCT and olive oil, supplementing with omega-3 fatty acid or carnitine while decreasing the intake of trans fat, saturated fat, and cholesterol; decreasing the KD ratio; and excluding all fatty meats, egg yolk, cream, butter, animal fat, palm oil and coconut oil; and using a solely formula-based KD.<sup>146–148</sup>

Although the risk for coronary artery disease may increase with long-term elevations of cholesterol levels, previous pediatric studies showed no change in the carotid intima-media thickness compared to baseline at 6 and 12 months of therapy.<sup>150,151</sup> On the other hand, local and systemic arterial stiffness was significantly increased in 2 studies involving children and young adults, correlated with serum cholesterol and triglycerides levels.<sup>152,153</sup> Nevertheless, long-term vascular outcomes of this high fat diet are not known.

Renal calculi historically have occurred in 3–7% of children on KDT.<sup>115,127,154</sup> They typically do not require KDT discontinuation and lithotripsy is necessary only rarely. As previously stated, oral citrates appear to help prevent stone formation.<sup>117</sup>

There is mixed data on the effect of KDT on growth in children. However, all six studies with longer than 6 months duration indicate that the classic KD has negative effects on growth, and over time may cause a height deceleration.<sup>84,138,139,155–157</sup> One retrospective review described 86% with slowed growth, and this effect was not related to age, KD duration, protein, or calorie intake.<sup>156</sup> A prospective study of 237 children found that the while older children grew “almost normally,” younger children had more difficulties.<sup>155</sup> A small change in protein, offered by the MCT diet, does not seem to result in better growth.<sup>84</sup>

Cardiac abnormalities have been reported in children on the KD, including cardiomyopathy and prolonged QT interval.<sup>124,125,158,159</sup> The mechanism of these complications is not fully understood; one case was associated with selenium deficiency, but others were not. As stated previously, routine ECG is not recommended at this time as a screening test. Pancreatitis has also been reported.<sup>129,160</sup> Hepatic dysfunction may be more likely to occur in children who are on both valproic acid and KDT, with intercurrent viral illness furthering increasing the risk of elevated transaminases.<sup>112,129,142</sup>

The long-term complications in children maintained on KDT for >2 years have not been reviewed systematically; there is only one report in the literature looking at this small subgroup.<sup>149</sup> In this population, there was a higher risk of



bone fractures, kidney stones, and decreased growth, but dyslipidemia was not identified.<sup>149</sup>

#### *Committee conclusions*

Like all medical therapies KDTs have potential adverse effects. Overall, the risk of serious adverse events is low; KDTs do not need to be discontinued for most adverse effects. Gastrointestinal complaints are often the most common but can be mostly remedied.

#### **Discontinuation**

The timing and actual method of KDT discontinuation are often individualized according to patient response. As stated previously, the consensus group agreed that KDT should be used for at least a mean of 3.2 months (SD 1.3 months) in order to make a fair assessment of efficacy, before considering discontinuation. Recent data suggest that KDT works rapidly when effective, with 75% of children responding within 14 days, so shorter diet durations may be adequate in some patients to assess if seizure reduction will occur.<sup>103</sup> Another study has shown that seizure freedom, although most likely to happen in the first few months, may occur as late as 18 months into KDT.<sup>161</sup> Should seizures worsen for >1–2 weeks after starting KDT, similar to ASDs, it could be discontinued immediately. If a family chooses to keep their child on KDT for longer than 6 months despite no apparent seizure control, the decision is ultimately theirs and should be supported as long as adverse effects are monitored and addressed.

In children with >50% seizure reduction, KDTs are often discontinued after approximately 2 years; however, in children in whom seizure control is nearly complete (eg, >90% seizure reduction) and side effects are low, KDTs can be continued for several years. There is no maximum duration for KDT. The consensus group recommends that KDT risks and benefits be reconsidered, however, at each clinic visit and certainly after ~2 years of continuous use (median 1.9 years, SD 0.6 years).

There are some conditions in which the 2-year KDT goal may be shortened or extended. In Glut-1DS, it is recommended that the KD be maintained at least until puberty but it can be useful long-term into adulthood.<sup>27,32,162</sup> Children with infantile spasms may require a shorter KDT duration. In research investigating the use of the classic KD for new-onset infantile spasms, 56% became spasm-free within 2 weeks of treatment.<sup>40</sup> Those who became spasm-free were maintained on the KD for 6 months and then the KD was discontinued without recurrence of spasms. All of these children had a normal EEG within 2 months of beginning treatment.<sup>40</sup> In a randomized study of medically refractory infantile spasms, early tapering of the KD at 6 months in children who became seizure-free with the KD had the same recurrence rate >1 year after discontinuation compared with children who used the diet for 2 years.<sup>163</sup> In addition, shorter periods of KDT use

have been reported for successful treatment of refractory status epilepticus.<sup>44,53</sup>

A large percentage, 80%, of children who are seizure-free on KDT will remain that way after KDT is discontinued.<sup>164</sup> The risk may be higher in those with discharges on EEG, brain malformations, and tuberous sclerosis complex.<sup>164</sup> In a multicenter study from Argentina, seizures recurred in 25% of those who were seizure-free and stopped the KD, with a median period of follow-up after discontinuation of the KD of 6 years.<sup>144</sup> Many of these children with recurrent seizures had brain lesions and EEG abnormalities.<sup>144</sup>

Although the classic KD can be discontinued abruptly in an emergency, preferably in an inpatient setting, it is more often reduced gradually over several months. The ratio can be reduced by 1:1 each month (eg, 4:1 to 3:1 to 2:1), followed by reintroducing regular foods and unlimited calories until ketosis is lost. During this period, the consensus group recommends continued nutritional supplementation. If seizures worsen, the KD can be increased to the previously effective ratio. In a recent study focusing on KD discontinuation, 14% of the children had increased seizures during the discontinuation period.<sup>165</sup> There was no significant difference in the incidence of seizure worsening during the weaning process based on the speed of discontinuation. Nevertheless, children who had 50–99% seizure reduction had a 3 times higher risk of increased seizures during weaning compared to seizure-free children, especially those with a higher number of active ASDs.<sup>165</sup> These children should have KDT discontinued with caution. They concluded that a 4- to 6-week discontinuation is feasible and well-tolerated. KDT tapering over days could also be done in some children without obvious benefit from KDT. For those in whom seizures worsened with KD discontinuation, the rate of seizure control recovery was similar (nearly 90% improved) between diet and ASD adjustments.<sup>165</sup>

The benefits of KDT can be seen long term, even in those who stopped it years prior.<sup>149,166</sup> For patients in whom the classic KD proves useful and necessary long-term, it may be reasonable to consider changing to the MAD or LGIT after several years. With increasing implementation of KDT in adolescents and adults, especially with the more liberal forms, and the occasional need or desire for prolonged use of KDT, there is a need for appropriate transitioning of KDT-related care. Adult epilepsy diet centers are the ideal option when available.<sup>23</sup>

#### *Committee conclusions*

Consideration should be given to discontinuing KDT after 3 months if unsuccessful, and at 2 years for cases in which there has been benefit. Shorter durations may be appropriate for patients with infantile spasms and status epilepticus, but longer diet durations are likely necessary for Glut1DS and PDHD and may be also appropriate based on individual responses for other forms of intractable epilepsy. Prior to KDT discontinuation in seizure-free children,

routine EEG may be valuable to counsel families regarding recurrence risk. During discontinuation, the consensus group generally recommends a gradual wean over 1–3 months, unless an urgent discontinuation is indicated.

### Clinical implications of translational ketogenic diet research

Over the past decade, there has been a steady increase in knowledge about the basic mechanisms underlying the clinical efficacy of KDT.<sup>167,168</sup> Given that KDTs are fundamentally metabolism-based treatments that induce a broad range of biochemical, hormonal, cellular, and physiological effects in an intact human or animal, it is not surprising that the relevant therapeutic mechanisms are likely multiple, parallel, and potentially synergistic.<sup>167,168</sup> Furthermore, although investigators have focused mainly on brain-specific effects of metabolic substrates and enzymes, there has been growing appreciation for the role of mediators outside the central nervous system, such as inflammatory targets.<sup>169</sup> Among the many hypotheses advanced over the years, the most compelling have invoked changes in neurotransmitter systems (ie,  $\gamma$ -aminobutyric acid [GABA], glutamate, and adenosine), metabolic coupling (eg, though ATP-sensitive potassium channels), glycolytic restriction, or diversion to the pentose phosphate shunt, inhibitory effects of fatty acids (eg, decanoate), enhancement of tricarboxylic acid (TCA) cycle function, and improved cellular bioenergetics and mitochondrial function (which can lead to a reduction in oxidative stress). All of these factors contribute to our understanding of the scientific basis of KDT action.<sup>167,168</sup>

In addition to understanding the neurobiology of KDT, the ultimate goals of such basic-translational research have been to reveal potential novel therapeutic targets for experimental therapeutics, and to evolve clinical formulations of the KD to enhance efficacy and tolerability.<sup>170</sup> However, the clinical implications, if any, of this knowledge are uncertain. One long-standing question is whether ketone (BOH) levels correlate with seizure control, that is, whether BOH is a biomarker for KDT effectiveness. This question remains unresolved as earlier clinical and animal studies have shown an inconsistent relationship (although recent data might suggest otherwise<sup>136</sup>). A second question is

whether ketogenic ratios and types of fats matter for clinical efficacy. To date, it is unclear whether certain ratios afford greater seizure protection than others in animal models, whereas in the clinical setting, higher ratios are generally associated with more favorable seizure control. With respect to polyunsaturated fatty acids (PUFAs) and medium-chain triglycerides (or MCTs), laboratory studies have inconsistently shown antiseizure/anti-excitability effects, and the human data are either unconvincing or not yet forthcoming. In addition, it appears that the classic KD formulation is equivalent to the MCT KD in terms of overall antiseizure efficacy.<sup>83</sup>

Glucose restriction is yet another approach that has been shown in animal models to block seizure activity, and perhaps even epileptogenesis.<sup>171</sup> The most encouraging evidence of this paradigm is the current preclinical development of 2-deoxyglucose (2-DG), a glycolytic inhibitor, spurred by the classic observation of reduced blood glucose levels in patients successfully treated with the KD.<sup>172</sup> Can the effectiveness of the KD be enhanced by adjunctive therapy with agents such as 2-DG or antidiabetic drugs such as metformin? The answer is not yet clear. Finally, anaplerosis (replenishing TCA cycle intermediates, eg, through triheptanoin supplementation) has been shown to favorably restore bioenergetic function and prevent ictogenesis in both laboratory models and humans with Glut1DS.<sup>33,173</sup> Could these findings be extended broadly beyond Glut1DS? Current evidence would suggest so. In the end, despite the compelling nature of these and other therapeutic approaches grounded in mounting scientific rationale, human clinical validation is required to enhance or transform current dietary approaches toward the treatment of epilepsy. At present, our enhanced understanding of KD mechanisms of action has yet to demonstrably affect clinical care, but the future looks promising.

## DISCUSSION

This consensus statement represents the second international effort to identify commonalities in the clinical use of KDT. As with the first consensus guideline, the majority of this group agreed on most of the major issues in choosing the best candidates for KDT, counseling families before

**Table 7. Selected survey responses from the initial (2009) consensus statement and this revision, focusing on responses with differing results<sup>10</sup>**

| Topic surveyed                     | Initial consensus response <sup>10</sup> (%) | Current consensus (%) |
|------------------------------------|--|-----------------------|
| Fasting mandatory?                 | 11   | 0                     |
| Outpatient approach feasible?      | 73   | 92                    |
| EEG at KDT discontinuation?        | 35   | 64                    |
| Monitor home BOH levels?           | 15   | 44                    |
| Empiric carnitine?                 | 8  | 16                    |
| Empiric oral citrates?             | (Not asked)                                  | 56                    |
| Offer KDT if surgery is an option? | 58   | 40                    |

starting, considering outpatient and nonfasting initiations, and basic supplementation. There was also consensus on most aspects of management of children on KDT with regard to clinic visit frequency, nutrition, laboratory values, potential side effects, and eventual discontinuation. Areas of variability included primarily supplements (oral citrates, vitamin D, selenium), use in children with surgically approachable lesions, and whether certain tests should be performed routinely (eg, DEXA, renal ultrasound, ECG, serum ketones, and EEG). Major changes since the prior consensus survey include fewer centers implementing fasting at KD onset, growth in evidence for alternative diets (MAD and LGIT) especially for adolescents, recommendation for a nonfasting classic KD approach only for children under 2 years of age, inclusion of a 1-month follow-up visit, and clarifications of ideal indications for KDT use (Table 7).

The creation of this consensus continues to demonstrate that multicenter and multinational KDT research protocols are feasible, including uniform dietary therapy management between research sites. In general, dietary therapies are provided similarly worldwide. Most evidence is Class III or IV, and further studies are recommended, especially for several areas of uncertainty where there was limited consensus.

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