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


2018 May 21;3(2):175-192
Guidelines on the ketogenic diet

• First attempt to create national consensus guidelines on KD: in Germany: paper published 2004 by Klepper et al

• Importance of guidelines were recognized: desire to evaluate research and best practice and create international guidelines

• 2006 The Charlie Foundation initiative for international committee of neurologists and dietitians with expertise in KDT
Beth Zupec-Kania  dietitian for the Charlie Foundation and
Eric Kossoff  MD, Director at Johns Hopkins Ketogenic Diet Center

• identified experts in clinical use of the KDT + had publication regarding KDT

• 26 clinicians: doctors and dieticians identified

• the original paper was published 2009
Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group


Epilepsia. 2009 Feb;50(2):304-17
New research and new clinical practice on KD
Update needed...

Revised consensus similarly organized by Eric Kossoff and Beth Zupec-Kania:

• Started 2017 planning of authors - all 26 previous authors were contacted to participate again. 4 declined.
• 9 new authors with recent publications on KD accepted to participate

This consensus includes 31 authors
• 6 (19%) are dietitians
• 17 (55%) from outside the USA: Canada 4, South America 2, Europe 7, Asia 4, Australia 1
Participants

• Did literature search and cited peer-reviewed publications when available

• Wrote a section either individually / in pairs based on their individual expertise and prior contributions

• In the absence of published literature, recommendations were based on the authors professional and center’s experience
Sharing expertise

• A survey=questionnaire sent to all 31 authors to obtain group opinion (like 2009)
  • The results of questions incorporated into the manuscript

• All authors reviewed, commented and suggested changes to the full manuscript prior to submission

• Dr James Wheeless, reviewed the document and assigned levels of evidence based on the available scientific information (utilizing the American Academy of Neurology classification of evidence for therapeutic interventions)

• The Charlie Foundation, Matthews Friends and Child Neurology Society reviewed and endorsed the manuscript
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CONSENSUS RECOMMENDATIONS

Patient selection

• **KDT considered** in a child who **failed 2 AEDs** regardless of age or gender. *Survey: mean after 2.6 AEDs, SD 0.9.*

• **Could** be offered earlier (when data suggest 20% better efficacy than the norm of KDT=40-50% responders in ≥ 3 publications and in ≥ 2 center): Angelman syndrome, Dravet syndrome, Infantile spasms, epilepsy w. myoclonic-atonic seizures, Tuberous sclerosis, FIRES/ super-refractory SE, formula-fed infants

• **Treatment of choice** for: Glut-1DS and PDHD (Pyruvate dehydrogenase deficiency syndrome)

• **Mixed opinion** regarding using KD in a child with an approachable surgical lesion. *Survey: 40% offer KDT, some for 3-6 mo trial. In 2009:58%!*
Patient selection

• Before diet start: **rule out inborn errors of metabolism** that could lead to a severe metabolic crisis - including disorders of fatty acid mitochondrial transport, β-oxidation defects

• Other indications as autism spectrum disorders, brain tumors, traumatic brain injury: **growing but insufficient evidence** of use of KDT other than in trials
Pre-diet evaluation and counseling

Counseling
• Clinic visit: seizure type(s), rule out contraindications, complicating comorbidities
• Discuss expectations on seizure reduction, medication and cognition
• Review anticonvulsants and other medications for carbohydrate content
• Recommend family to read parent-oriented KDT information

Nutritional evaluation
• Baseline weight, height, and ideal weight for stature, (BMI)
• Head circumference - infants
• 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, LGIT)
• Calculation of calories, fluid, and ketogenic ratio
• Establish vitamin + mineral supplementation based on Dietary Reference Intake
Pre-diet evaluation and counseling

Laboratory evaluation blood and urine

• Blood count with platelets
• Electrolytes, bicarbonate, total protein, calcium
• Liver and kidney tests (including albumin, AST, ALT, blood urea nitrogen, creatinine)
• Fasting lipid profile
• Acylcarnitine profile
• Vitamin D level
• Urine analysis
• Anticonvulsant levels (if applicable)
Pre-diet evaluation and counseling

Optional testing

• EEG
• MRI
• EKG (echocardiogram), strongly consider if history of heart disease
• Urine organic acids (if diagnosis unclear)
• Serum amino acids (if diagnosis unclear)
Pre-diet evaluation and counseling

- Dietary therapy should be provided for **at least 3 months** before considering the therapy non-efficacious and discontinuing KDT

- Key component of success: Information before start.....

- Ketogenic nurse of outmost importance to help family with transition to the diet
Specific Diet Selection and Provision

• Choose specific KDT based on
  - dietary needs/habits of the individual child
  - expertise of the KDT center

• No evidence of different efficacy of classic and MCT diet (class III evidence)
• Liquid/ formula-based KD - recommended in infants not yet on solid foods + children fed enterally

• Children < 2 years should be started on classic KD (class III evidence)
• MAD and LGIT recommended for adolescents (classic KD for individual cases!)

• Calorie and fluid restriction no longer recommended (no evidence of better efficacy)
Initiation of Dietary Therapies

• **Flexibility** at diet start is supported by clinical studies

• Fasting - majority of the consensus group: no longer fasting
• Fasting *may* be used: if quick time to response needed. More immediate side effects!

• The classic KD **can** be started as an outpatient, but most centers routinely admit for initiation. *Survey: 80% admit for start*

• The MAD and LGIT are **typically** started as an outpatient without a fasting period
Concurrent AEDs

- Little evidence of positive pharmaco-dynamic interactions between KDT and AEDs
- KDT not negatively affected concerning efficacy by any particular AED
  (1! study lamotrigine associated lower efficacy/ketones)

- Pharmaco-kinetic interactions - serum levels of AEDs do not seem significantly altered by KDT
- Monitor drug levels before and at follow-up and if side effects

- Topiramate, zonisamide, acetazolamide - may worsen metabolic acidosis and risk kidney stones
- AEDs may be reduced after 1 month if KDT is successful. (!?) Caution when reducing phenobarbital or benzodiazepines!
Supplementation

• Evidence for use of multivitamin and mineral supplements (low-carbohydrate!) in the routine use of KDT

• Oral citrates appear to prevent kidney stones (Class III evidence. One study reduced incidence 6.7 → 0.9%). Mixed opinion on empiric use!

• Vitamin D levels decrease on the KD. Split opinions on empiric supplementation!

• No recommendation on carnitine. Survey: 88% of centers check levels but 84% treat only if hypocarnitinemia / symptomatic cases

• No recommendation is given for use of antacids or laxatives
Supplementation

Universal recommendations
• Multivitamin with minerals (including trace minerals + selenium) (Studies: low Magnesium and selenium at 1 y on classic KD)
• Calcium and vitamin D - meeting daily RDA requirements

Optional extra supplementation
• Vitamin D (above RDA) (Survey: 52% give additional vitamin D)
• Additional magnesium, selenium, zinc, phosphorus, iron, copper. (Survey: 44% give additional selenium)
• Oral citrates (CitraK™ or PolycitraK™) (Survey: 56% give oral citrates)
• Carnitine
• Laxatives: Miralax™, mineral oil, glycerin suppository
• MCT oil, coconut oil, omega 3
Follow-up visits of children on dietary therapies

• Visits at 1, 3, 6, 9, and 12 months on KDT in the 1st year. Then visits every 6 months.

• More frequent contacts: infants + patients at high risk for nutritional deficiency.

• All children should be seen by a team experienced in KDT: pediatric neurologist + dietitian + nurse/coordinator.

• All should have nutritional assessment + laboratory evaluation + discussion on KDT and AED discontinuation.

• Consider an EEG prior to KDT discontinuation.
At home

• Urine ketones checked several times / week
• Studies shown: better correlation to seizure control with blood beta-hydroxybutyrate (B-OH) level than urine
• Home (B-OH) level: More expensive and fingersticks. *Survey: Used by 44% of centers*

• No recommendation on type of ketone monitoring
At Follow-up visits

Nutritional assessment (registered dietitian)
- Height, weight, ideal weight for stature, growth velocity
- Head circumference - in infants
- Review appropriateness of KDT prescription (calories, protein, and fluid)
- Review vitamin + mineral supplementation
- Assess compliance + Adjust KDT if necessary to improve compliance and seizure control

Medical evaluation (neurologist)
- Efficacy of the diet (is the KDT meeting parental expectations?)
- Side effects of KDT?
- AED dose reduction (if applicable)
- Should KDT be continued?
At Follow-up visits

**Laboratory assessment**
- Complete blood count with platelets
- Electrolytes, serum bicarbonate, total protein, calcium
- Liver and kidney profile (including albumin, AST, ALT, blood urea nitrogen, creatinine)
- Vitamin D level
- Fasting lipid profile
- Free and total carnitine
- Urinalysis
- Selenium level
- Anticonvulsant drug levels (if applicable)
- EEG (consider at KDT discontinuation)
At Follow-up visits

**Optional**

- Serum beta-hydroxybutyrate (B-OH) level
- Zinc, copper levels

- Renal ultrasound. *Survey: routine in 40%*
- EKG. *Survey: routine in 40%*
- Bone mineral density (DEXA scan) if > 2 years on KD. *Survey: in 48%*
Adverse effects

• Gastrointestinal – most common. *Often treatable!*
• Hyperlipidemia – in 14-59%, often temporary. *Adjust type of fat or ratio!*
• Coronary artery disease – studies shown arterial stiffness, longterm vascular outcome not known
• Renal calculi – historically in 3-7%. Studies: *Oral citrate appear to prevent!*
• Growth velocity – most studies show height deceleration espec. young children

• Risk of serious adverse events is low. KDT seldom need to be discontinued due to adverse effects
Discontinuation

• If KDT unsuccessful after 3 months – usually discontinue
• If good efficacy – taper after 2 years

• Shorter durations – Infantile spasms and status epilepticus
• Longer durations for Glut-1DS + PDHD + intractable epilepsy based on individual responses. Later consider MAD or LGIT!

• Prior to KDT discontinuation in seizure-free children → consider a routine EEG to counsel families regarding recurrence risk

• Discontinuation with gradual wean over 1-3 months, unless urgent stop is needed
Consensus

most aspects of management of children on KDT: clinic visit frequency, nutrition, laboratory values, potential side effects, and eventual discontinuation

Disagreement/variability concerning

• supplements (oral citrates, vitamin D, selenium)
• use in children with surgically-approachable lesions
• if tests should be performed routinely (e.g. DEXA, renal ultrasound, EKG, serum ketones and EEG)
Selected responses in questionnaire 2009 and current

<table>
<thead>
<tr>
<th>Topic</th>
<th>2009 consensus response</th>
<th>Current consensus</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fasting mandatory?</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>• Outpatient approach feasible?</td>
<td>73%</td>
<td>92%</td>
</tr>
<tr>
<td>• EEG at KDT discontinuation?</td>
<td>35%</td>
<td>64%</td>
</tr>
<tr>
<td>• Monitor home B-OH levels?</td>
<td>15%</td>
<td>44%</td>
</tr>
<tr>
<td>• Empiric carnitine?</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>• Empiric citrate?</td>
<td>Not asked</td>
<td>56%</td>
</tr>
<tr>
<td>• Offer KDT if surgery is an option?</td>
<td>58%</td>
<td>40%</td>
</tr>
</tbody>
</table>
Major changes since the prior consensus paper:

• Fewer centers implement fasting at KD onset
• Growth in evidence for alternative diets (MAD and LGIT), especially for adolescents
• Recommendation for classic KD only for children below 2 years
• Inclusion of a 1-month follow-up visit
• Clarifications of ideal indications for KDT use
Thank you for your attention!