The Present and Future of the Ketogenic Diet as it Approaches its Second Century!

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Disclosures

- Consultant: Nutricia, Atkins Nutritionals, Bloom Science, Vitaflo, Greenwich
- Data Safety Boards: NIH, BioPharm, Greenwich
- Royalties: UpToDate, Demos, Oxford Press

Dr. Kossoff is a world-renowned neurologist who has been invited to speak for his expertise on the ketogenic diet. The opinions reflected in this presentation are solely those of Dr. Kossoff and independent of Nutricia North America.
July 27, 1921

Dr. Wilder at Mayo Clinic, Rochester, MN creates a high fat, low carbohydrate diet to mimic fasting state.
PubMed: “Ketogenic”

![Graph showing the trend of PubMed entries related to "Ketogenic" over time.]

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Epilepsia Open
The Open Access Journal of the International League Against Epilepsy

SPECIAL REPORT

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


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Topics

1. Latest research towards clinical use and flexibility in 2020

2. Keto in Covid-19 pandemic?

3. Future directions in the next century
**The Traditional Method of Starting the Ketogenic Diet**

- Traditionally started in the hospital over 2-4 days, following a 24 hour fast
- Dietitians calculate ratio (fat: protein and carbs), calories, fluids
- Foods weighed and measured

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**Four Ketogenic Diets**

<table>
<thead>
<tr>
<th>Standard “Normal” Diet</th>
<th>Ketogenic Diet</th>
<th>Medium Chain Triglyceride Diet</th>
<th>Modified Atkins Diet</th>
<th>Low Glycemic Index Treatment</th>
</tr>
</thead>
</table>

- Carbohydrates
- Protein
- Fat

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Flexibility!

- Seminal paper by Dr. Christina Bergqvist published in *Epilepsia* in 2005
- No difference in a randomized trial between fasting and “gradual” onset
  - Outcomes identical at 3 months

- No reason to fluid or calorie restrict
- All 4 diets equally valid: you choose!
  - KD for < 2 years, MAD/LGIT for > 12 years
- Admission? 92% believe it’s optional
- Fasting? 68% believe it’s optional
  - Not in infants < 2 years
Major Changes: Revised Consensus

• **New “true” indications (>70% response rates)**
  – Angelman syndrome, Complex 1 mitochondrial disease, FiRES, Ohtahara syndrome, super-refractory status epilepticus

• **Remaining on the list:**
  – Dravet syndrome, Doose syndrome, Glut-1, formula-fed children, infantile spasms, pyruvate dehydrogenase deficiency, tuberous sclerosis complex

• **Helpful (40-70% response, but not “indications” currently):**
  – Adenylosuccinate lyase deficiency, CDKL5 encephalopathy, Childhood absence epilepsy, Cortical malformations, Epilepsy of infancy with migrating focal seizures, ESES, Glycogenosis type V, Juvenile myoclonic epilepsy, Lafora body disease, Landau-Kleffner syndrome, Lennox-Gastaut syndrome, Phosphofructokinase deficiency, Rett syndrome, Subacute sclerosing panencephalitis (SSPE)

“Hot” Indications in 2020

- Status epilepticus
- TPN
- Infants and infantile spasms

*There are no nutritionally complete ketogenic formulas approved for infant use in the United States of America.*
<table>
<thead>
<tr>
<th>Ref</th>
<th>Author</th>
<th>Age</th>
<th>Diet</th>
<th>Etiology</th>
<th>Response (days (%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>Francois</td>
<td>6</td>
<td>EN KD</td>
<td>RSE</td>
<td>50%</td>
</tr>
<tr>
<td>2006</td>
<td>Mikaeloff</td>
<td>1</td>
<td>EN KD</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Chevret</td>
<td>1</td>
<td>EN KD</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>2008</td>
<td>Bodenant</td>
<td>1</td>
<td>EN KD</td>
<td>Focal epilepsy</td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Paperback</td>
<td>2</td>
<td>EN KD</td>
<td>Partial foci, tuberculoma</td>
<td>90</td>
</tr>
<tr>
<td>2008</td>
<td>Needham</td>
<td>2</td>
<td>EN KD</td>
<td>Rasmussen, focal trauma</td>
<td>8 (6)</td>
</tr>
<tr>
<td>2008</td>
<td>Berndl</td>
<td>4</td>
<td>EN KD</td>
<td>Focal, tuberculoma related syndrome*</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Bervenkott</td>
<td>1</td>
<td>EN KD</td>
<td>Malignant, possible metastasis</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td>Nabbout</td>
<td>9</td>
<td>EN KD</td>
<td>Febrile infection-related syndrome*</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Villeneuve</td>
<td>5</td>
<td>EN KD</td>
<td>SWS, encephalitis, cryptogenic</td>
<td>1-10</td>
</tr>
<tr>
<td>2009</td>
<td>Kumada</td>
<td>2</td>
<td>Oral MAD</td>
<td>Frontal lobe, heterotopia</td>
<td>5-10</td>
</tr>
<tr>
<td>2010</td>
<td>Wusthoff</td>
<td>2</td>
<td>EN KD</td>
<td>Rasmussen, head trauma</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Nabbout</td>
<td>9</td>
<td>EN KD</td>
<td>Febrile infection-related syndrome*</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Cervenka</td>
<td>1</td>
<td>EN KD</td>
<td>Idiopathic, possible autoimmune</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Lin</td>
<td>1</td>
<td>IV KD</td>
<td>Focal epilepsy</td>
<td>3</td>
</tr>
<tr>
<td>2011</td>
<td>Caraballo</td>
<td>2</td>
<td>EN KD</td>
<td>Refractory myoclonic status epilepsy</td>
<td>75-90% and 50% reduction</td>
</tr>
<tr>
<td>2015</td>
<td>Incecik</td>
<td>1</td>
<td>EN KD</td>
<td>CP No</td>
<td></td>
</tr>
<tr>
<td>2015</td>
<td>Amer</td>
<td>1</td>
<td>EN KD</td>
<td>NMDA encephalitis</td>
<td>14</td>
</tr>
<tr>
<td>2016</td>
<td>Cervenka</td>
<td>15</td>
<td>EN KD</td>
<td>SRSE - 5 NORSE, 3 ICH, 2 LGS, 2 anoxic, 1 GBM, 1 TBI, 1 encephalitis</td>
<td>0-10 (73%)</td>
</tr>
</tbody>
</table>

**ICU Protocol**

- Remove dextrose from intravenous fluids
- D/C current enteral formula
- Remove carbohydrates from medications and parenteral fluids
- Check fasting lipid profile, CMP, CBC, selenium levels, urine ketones
- Nutrition consult
- Begin 4:1 formula at half RDA of calories for first 24 hours then advance to full calories
- Begin multivitamin and calcium via GT/NG crushed and mixed in water
- Document baseline weight and height
- Check glucose every 6 hours
- Consider wean of pentobarbital drip after 1 week

*Courtesy Mackenzie Cervenka, MD*
2 Important Guidelines

Elles van der Louw 1, Vanessa Aldaz 2, Jessica Harvey 3, Marian Roan 4, Dorine van den Hurk 5, J Helen Cross 6, Stéphane Auvin 7, Review Group

Survey of 150 centers, 35 patients in the literature reported

Elles van der Louw, Dorine van den Hurk, Elizabeth Neal, Barbel Leiendecker, Georgiana Fitzsimmon, Laura Dority, Lindsey Thompson, Maddelena Marchio, Magdalena Dudzinska, Anastasia Dressler, Joerg Klepper, Stephane Auvin, J Helen Cross.

15 expert review, consensus guideline format, best evidence

*There are no nutritionally complete ketogenic formulas approved for infant use in the United States of America.

Breastfeeding?

• Frequent posters at AES and the biannual keto meetings

• Le Pichon et al. Seizure 2019
  – 9 infants
  – Breastmilk expressed and mixed with 4:1 ketogenic or a soy-based formula

• Dressler et al. Breastfeed Med 2020
  – 16 infants
  – Similar protocol to Le Pichon, but several breastfed after bottle feed

*There are no nutritionally complete ketogenic formulas approved for infant use in the United States of America.

* 13 studies, 341 patients selected for analysis
  
  - 65% with >50% spasm reduction
  - 35% spasm-free
  - IS due to unknown etiology higher chance of seizure-freedom (RR 1.72)

*There are no nutritionally complete ketogenic formulas approved for infant use in the United States of America.*

- 101 infants, RCT and parallel-cohort, *included those treated with vigabatrin before*

- All infants: 47% KD vs. 48% ACTH
  - Relapse rate 16% KD vs. 43% ACTH (p=0.09)

- For New Onset *(no prior vigabatrin)*:
  - At 1 month: 80% ACTH vs. 47% KD (p=0.02)
  - At last visit: 21% ACTH vs. 48% KD (p=0.05)

*There are no nutritionally complete ketogenic formulas approved for infant use in the United States of America.*
KD for New-onset Spasms Today

- I will offer it when infants present within 2 weeks of onset

- 13/28 patients tried (46%)
  - When not successful, parents still very appreciative

- Need an eager team

- Most common reasons for refusal:
  - Ease of oral steroids and I’m not on call

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Several potential options!! It’s Possible!

1. Classic KD by Zoom as an outpatient

2. Modified Atkins Diet (with information emailed, video links given)

3. Admit anyway with in-person, Zoom, or phone education
   - Abbreviated admits

Continuing KDT in a pandemic

**Telemedicine!**

Make sure there's a home scale

High fat, canned foods with long shelf-lives
  - Oils, tuna, mayo, nuts
  - May need special notes for milk, eggs, meat

Food delivery services?

90 day supplies of vitamins, formulas, supplements (and medications)

Lock away high carb foods...

Don’t worry as much about labs
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JHH Adult Epilepsy Diet Center

• Approaching the 10 year anniversary!

• >300 adults seen in clinic to date
  – ~20% were already on diet therapies at initial visit
  – ~80% were not started on modified Atkins diet

Slide courtesy Dr. Mackenzie Cervenka
3-month Seizure Outcomes in Adults

Select Unanswered Questions in Adults

- How do we improve compliance?
  - Ketone esters, MCT, set recipes, pre-made foods

- What are the ramifications of elevated lipid profiles in adults?

- Is the diet safe in pregnancy?

- Many more!
Gut Microbiome

• Akkermansia muciniphila and Parabacteroides together
  – Changes within 4 days in mice on the KD
  – Providing these bacteria after antibiotics restored seizure protection

• Under active study in humans
Neurologic Uses Other than Epilepsy

Hypoxia-anoxia 2001
Autism 2003
Brain tumors 2003
Depression 2004
Narcolepsy 2004
Glycogenosis Type V 2005
Alzheimer's 2005
Traumatic brain injury 2005
Parkinson's 2005
ALS 2006
Migraine 2006
Sleep disorders 2007
Post hypoxic myoclonus 2007
Schizophrenia 2009
Spinal cord injury 2009
Pain 2009
Sandhoff disease 2010
Huntington's disease 2011
Bipolar disorder 2012
Multiple Sclerosis 2012
Diving CNS toxicity 2014
Alternating hemiplegia of childhood 2015
Kabuki syndrome 2016
Pelizaeus-Merzbacher disease 2019

Ongoing research continues in these areas


FIGURE 1. Timeline of studies utilizing a ketogenic diet for cancer treatment. After Wilhelm Brünings’ pioneering studies, it took 70 years until interest in the ketogenic diet re-emerged as exemplified by an increasing number of published studies beginning in 2011. Reproduced from ref. [2*], which was published under a creative commons license CC BY-NC-ND 4.0.

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Ongoing research continues in this area
Unanswered questions for alternative indications?

- Are the mechanisms of action different for each indication?
- Will they truly be effective?
- Will patients stick to the diet for a chronic illness without distinct calendar “events”?
- Who will do the research?

Table 1. Hypothesized mechanisms through which ketogenic therapies influence neurological disease.

<table>
<thead>
<tr>
<th>Ketogenic Mechanisms</th>
<th>Epilepsy</th>
<th>Malignant Glioma</th>
<th>Alzheimer’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic Regulation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose uptake &amp; glycolysis</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Insulin, IGF1 signaling</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ketones/ketone metabolism</td>
<td>+</td>
<td></td>
<td>+</td>
</tr>
<tr>
<td>Altered gut microbiota</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neurotransmission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Altered balance of excitatory/inhibitory neurotransmitters</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition of AMPA receptors</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mTOR activation &amp; signaling</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Modulation of ATP-sensitive potassium channels</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oxidative Stress</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Production of reactive oxygen species</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Mitochondrial biogenesis/function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inflammation/Neuroprotection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammatory cytokines</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>NLRP3 inflammasome inhibition</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>TRYPTIC T cell function</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>peritumoral edema</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>amyloid-β levels</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Genomic Effects</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibition of HDACs</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>PPARy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Expression of angiogenic factors in tumor cells</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

AMPAR—α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; IGF1—insulin-like growth factor 1; HDACs—histone deacetylases; mTOR—mammalian target of rapamycin; NLRP3—NOD-like receptor protein 3; PPAR—peroxisome proliferator-activated receptor. $-$ decreased; $?$—increased; $+$—mechanism shown in *in vivo* or *in vitro* studies.

Table from McDonald TJW, Cervenka MC. The Expanding Role of Ketogenic Diets in Adult Neurological Disorders. Brain Sci. 2018;8.

Ongoing research continues in these areas.
Consensus Guided Future Research: 2028

• Supplements
• Children with surgically-approachable lesions
• DEXA and monitoring for long-term risks?
• Value of EEG
• Serum ketones? Necessary?
• First-line use before medications
**Epilepsy Research KD Special Issue 2020**

- Dressler A, Trimmel-Schwahofer P. The ketogenic diet for infants: How low can you go?
- Armeno M, Caraballo R. The evolving indications of KD therapy.
- Husari KS, Cervenka MC. The ketogenic diet all grown up: Ketogenic diet therapies for adults.
- *(and 4 basic science articles courtesy of Dr. Jong Rho coming soon!)*