What, why and how to use the ketogenic diet

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## Disclosures

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The ketogenic diet

What is it?

A high fat diet, designed to mimic the metabolic effects of starvation, used in the treatment of epilepsy.

Not a natural treatment
Data available

Lefevre and Aronson 2000
Systematic review of 11 studies
All 11 observational; only 2 prospective
Uncontrolled studies 9/11 from single institution
Old treatment

.....new lease of life
Normal UK diet, classical KD and MCT KD

- Normal
  - Fat: 35%
  - Protein: 15%
  - Carbohydrate: 50%

- Classical
  - Fat: 90%
  - Protein: 6%
  - Carbohydrate: 4%

- MCT
  - Fat: 73% (30-60% MCT)
  - Protein: 10%
  - Carbohydrate: 17%
Evidence base for efficacy?


- 4 RCT; 5 publications
- Recruited total 289 children
- Despite the heterogeneity, all trials showed that at least 38% of patients had a 50% reduction in seizures compared to their comparative controls at three months, and this response was maintained for up to a year.
Syndrome efficacy

- West syndrome/infantile spasms
  - Newly diagnosed *Kossoff et al Epilepsia* 2008;1504-1509

- Dravet syndrome
  - Compared to suboptimal treatment *Caraballo et al Epilepsia* 2005;46:1539-44
  - Following optimal treatment *Nabbout et al Epilepsia* 2011;52:e54-7

- Lennox Gastaut Syndrome
  - 47% >50% reduction 3-36m
    *Lemmon et al Dev Med Child Neurol* 2012;54:464-8

- Myoclonic astatic epilepsy
  - Specific responsiveness *Oguni et al 2002, Kirau & Bergqvist 2007*
Glut 1 Deficiency

• Glut 1; 1 of 9 glucose transporters. Coded by SLC2A1

• Wide range clinical presentation – early onset absence epilepsy to later onset movement disorder

• Treatment with ketogenic diet
  – 86% epilepsy respond to KD
  – Less frequent for movement disorder

  *Leen et al Brain 2010;133:655-70*

• Early diagnosis and intiation of KD may improve outcome

  *Ramm-Pettersen et al Dev Med Child Neurol 2013;55:440-447*
What about adults?

The ketogenic and related diets in adolescents and adults
Payne et al Epilepsia 2011;52:1941-1948

- 122 adults/82 adolescents open label on KD
- 56 adults/10 adolescents MAD
- Sides effects similar to children, main reason for discontinuation lack of efficacy

Efficacy & compliance; a meta-analysis

- 12 studies, 270 patients
- Efficacy
  - All diets 42%
  - CKD 52%
  - MAD 34%
- Compliance
  - All diets 45%
  - CKD 38%
  - MAD 56%
What about implementation?
December 2006, Charlie Foundation, commissioned panel of 26 pediatric epileptologists & dieticians from 9 countries

Consensus statement

Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group


Endorsed by the Practice Committee of the Child Neurology Society
Specific diet selection & provision

- KD diet chosen should be based on dietary needs & habits of individual child
- Formula vs solid based feed
- Preliminary evidence for less restrictive regimes
  - 42% consensus group believed these should be used for adolescents
Alternative diets?

**Atkins diet**
- High fat low carbohydrate diet
  - 20g CHO/day
- No amount restriction – aim to eat to satiety
- No protein restriction – free foods are high protein foods
  
  *Kossoff et al 2006, 2007*  
  *Kang et al 2007*

**Low GI diet**
- ‘Glycaemic Index’
  - Calculated from incremental area under blood glc curve after feeding indexed to ingested glc
- 76 children; 50% >50% reduction at 3m
- 49 discontinued after 2-108 weeks

*Sharma et al Epilepsia 2013;54:481*
- RCT 102 children 2-14 yrs
- MAD vs no change in treatment
- >90% seizure control 30% vs 7% p=0.005
- >50% seizure control 52% vs 11.5%, p<0.001

*Muzykewicz et al 2009*
Comparison of Ketogenic diet regimes

Classical 4:1 ratio

% energy
- Fat: 90%
- Protein: 4%
- CHO: 6%

MAD approx 1:1 ratio

% energy
- Fat: 65%
- Protein: 30%
- Carbohydrate: 5%
Dietary therapy of epilepsy

Ketosis

- KD 3:1
- KD 4:1
- MCT
- MAD
- LGIT

Infant | Pre-school | School age | Adolescent | Adult
Implementation

• Fasting
  – Gradual initiation protocols lead to similar seizure reduction at 3m
  – 58% consensus group believed fasting not necessary but had benefit

• Hospitalisation
  – 88% consensus group routinely admitted for initiation for safety & education

• Protocols at individual centres will depend on experience
Medications & the KD

- No data supporting any significant pharmacodynamic interactions with AEDs
- No specific concern with VPA
  - ?carnitine deficiency
- Carbonic anhydrase inhibitors
  - Early acidosis
  - No proven increased risk renal stones but caution, ?oral citrates
- Medications can often be reduced in first few months
- ? Works well in combination with VNS
Supplementation

• Universal understanding for use of low carbohydrate multivitamin & mineral supplementation

• Oral citrates preventative for kidney stones
  – *NB at risk groups*

• No evidence for empiric use of antacids, laxatives, or carnitine
Maintenance & monitoring

- 96% group advocated routine urine ketone evaluation by parents
  - Blood ketone monitoring increasingly used

- Ongoing clinic visits at least every three months
  - Experienced paediatric neurologist & dietician
  - Available ongoing contact with ‘KD team’
  - Less frequent beyond 12m

- More frequent visits may be required for infants and other patients at risk for nutritional deficiency

- Nutritional assessment, growth parameters, laboratory evaluation

- Assessment of medication

- ?moderation of classical ratio after 3m Seo et al 2007

- Each visit there to be full evaluation of risk/benefit to continuing with KD
Adverse effects

- Not a natural treatment – side effects do occur
  - risk low
- Metabolic abnormalities relatively minor
- Gastrointestinal symptoms 12-50%
  - majority alleviated with diet modification
- Renal calculi 3-7%
  - rarely require diet discontinuation
- Growth slowing
  - greater risk in younger children
  - no difference between diets
- Minimal data on long term effects

Consensus view ‘evaluate risk-benefit of continuation at all times’
Discontinuation of the diet

• Timing and method of KD discontinuation individualised based on patient response

• Consideration given to discontinuation
  – 3m if unsuccessful
  – 2 years if successful

• Where KD highly successful longer duration may be considered
  – GLUT1, PDHD, TS

• 80% SF on diet, likely to remain so on discontinuation
  – risk recurrence higher with epileptiform EEG, structural brain abnormality & TS (Martinez et al 2007)
  – 73% consensus group obtained EEG prior to discontinuation for counselling

• Gradual wean recommended over 2-3m
• A physician (preferably a neurologist) familiar with ketogenic diets is mandatory for a new ketogenic diet team with limited resources; a dietitian is mandatory for the classic ketogenic diet, but optional for the alternative diets.

• The minimum laboratory studies at baseline are serum sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, and glucose. Fasting lipid profile and urinalysis are to be included with followup labs.

• All patients should receive a multivitamin, calcium, and, if infants, have access to ketogenic diet formulas. Other supplements described in this article are recommended or optional.

• Admission to a hospital to start dietary therapies is recommended for infants or patients with comorbidities.
How should the diet be used?
The ketogenic diet improves recently worsened focal epilepsy

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AIM  We observed a dramatic response to the ketogenic diet in several patients with highly refractory epilepsy whose seizure frequency had recently worsened. This study aimed to identify whether this characteristic was a useful indication for the ketogenic diet.

METHOD  From the 70 patients who received the ketogenic diet during a 3-year period at our institution, we retrospectively selected patients with focal epilepsy. There were 22 children, 13 females and nine males, aged from 5 months to 18 years 6 months (mean 6y 9mo, SD 5y 11mo). Fifteen had symptomatic and seven had cryptogenic focal epilepsy. Seizure frequency 1 week before initiating the ketogenic diet was compared with that at 1 month and at the last visit on the diet.

RESULTS  Eleven patients were responders (defined as reduction of seizures by more than 50%) at 1 month. Responders were higher (p=0.046) in the group with a recent worsening of seizures than in those with stable seizure frequency. Seven patients were still seizure-free at 6 months on the diet. Tolerability was excellent in 10 patients. Five patients stopped the diet because of early side effects.

INTERPRETATION  The ketogenic diet may be a valuable therapeutic option for children with pharmacoresistant focal epilepsy, particularly those with a recent deterioration of seizure control and neurological status. Because of its rapid effect, the ketogenic diet may be a useful support to intravenous emergency drugs in such a situation.
Status epilepticus

- Anecdotal case reports of success
- Eg Nam et al Epilepsia 2011;52:e181-4
  - Refractory status epilepticus
  - Four children & one adult refractory to standard therapy
  - Seizure frequency decreased to <50% baseline median 8 days
  - At one month 2 SF, 1>90% reduction and 2>75%
  - High rate side effects
• 9 patients with FIRES treated with ketogenic diet over 12 years
• 7 responders – within 2-4 days ketonuria, 4-6 days of diet initiation
• One relapsed and died
• Others continued with seizures at a later date
The ketogenic diet in epilepsy 2015

- An old treatment with a *sustained* lease of life
- Good evidence utilisation of ketogenic diet in refractory childhood epilepsy
  - Wider resource – patient choice
- Specific situations where acute utilization justified
- Limited evidence that may be beneficial and applicable in adults
  - Role for more relaxed applications
- Global acceptance – enhanced choice