Ketogenic Fuelling; for adults with drug resistant epilepsy and beyond

Sue Wood RD,

Matthew's Friends Clinics,

UK

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Agenda

- History of ketogenic diet therapy
- What is a ketogenic diet
- Mechanisms of action
- Use in Status Epilepticus in adults
- Use in enteral adult patient
- Summary

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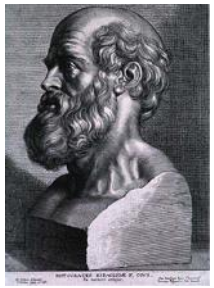


HISTORY OF KETOGENIC DIET THERAPY

The ketogenic diet – old news!

460 BC – Hippocrates

- body purification (fasting)



1921 Conklin, Geyelin

- fasting for 20-30 days
  Cure rate for epilepsy 87% (30 patients)

Woodyat , Wilder

- *'..benefits of fasting could be obtained if ketonemia was produced by other means'*
  The Classical Ketogenic Diet

1971 Huttenlocher

- Developed **MCT Ketogenic Diet**
  60% energy as Medium Chain Triglycerides; C 6-12.

2003 Kossoff / Theile & Pfeifer

- Developed **Modified Atkins Diet**
- **Low Glycaemic Index Treatment**

FASTING AS EPILEPSY CURE.

Osteopaths Hear That 22 Days on Water Usually End Fits.

LOS ANGELES, July 5.—Epilepsy may be cured by fasting, Dr. Hugh Conklin told the twenty-sixth annual convention of the American Osteopathic Association, now in session here. Epilepsy, according to Dr. Conklin, is caused by the improper functioning of certain glands in the bowels. By fasting for twenty-two days, taking only water, a cure may be effected, he said.

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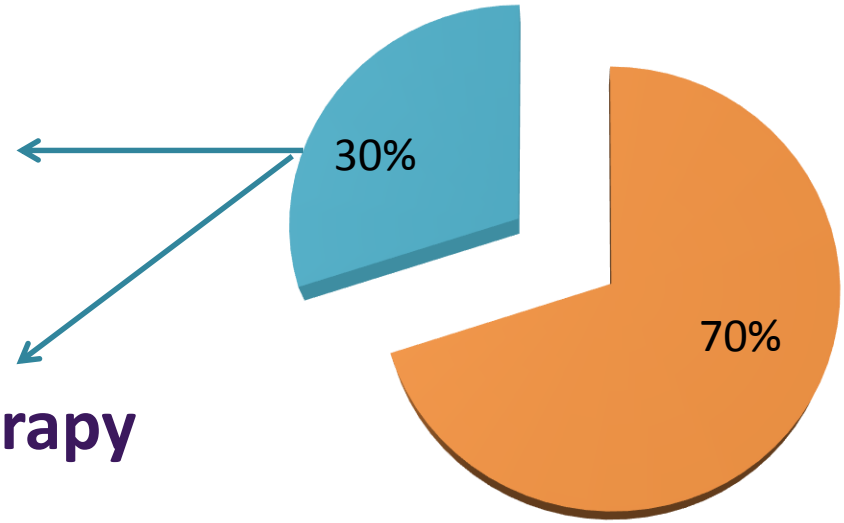
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25-30% of epilepsy cases = drug resistant

Other treatment options:

- **Vagal Nerve Stimulation**
- **Deep Brain Stimulation**
- **Epilepsy Surgery**



- **Ketogenic Dietary Therapy**
  - **Access for Children ☺**
  - **Little access for adults ☹**

Sillanpää & Schmidt, 2006

For children : improved provision ☺



- Resurgence in 1990's
- RCT evidence 2008[1]
- UK NICE Guidance[2]:
  "children & young people"
- 25 Paediatric keto teams[3]

- [1] Neal et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Lancet Neurol* 2008: 7:500-506
- [2]UK *NICE Guidance 137:* Epilepsies: diagnosis and management. https://www.nice.org.uk/guidance/cg137/chapter/1-guidance#ketogenic-diet
- [3] https://www.matthewsfriends.org/medical-section/keto-centres/

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For adults ; why so slow?

1930 Barborka (Mayo Clinic)

- Published data on 100 cases 15-51years.
- 56 gained >50 % reduction in seizures.

At this time KD was used equally for children & adults



2015 Fang Ye: Meta-Analysis

Efficacy of & Patient Compliance with KD (n=270)

"Comparable with paediatric efficacy"

"Potential to increase compliance!"

Fang Ye et al. Journal of Clinical Neurology 2015; 11(1):26-31

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WHAT IS A KETOGENIC DIET

A ketogenic diet

- **Low in carbohydrate** ***key driver*** *
- **High in fat**
- ***Adequate in* protein**

Medical therapy options:

- **Classical KD**
- **Medium Chain Triglyceride KD**
- **Modified Atkins Diet**
- **Modified KD (UK)[1]**
- **Low Glycaemic Index Treatment**

All individually prescribed, monitored and adjusted

1Understanding the core principles of a 'modified ketogenic diet': a UK and Ireland perspective. J Hum Martin-McGill KJ, et al. Nutr Diet. 2019 Jun;32(3):385-390.

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What does my ketogenic diet look like?

ENTERAL?

Example:



BASE FEED:
KETOCAL
2.5 LQ & 4:1 LQ



Extra protein?
Prosource TF,
Protifar



Extra CHO?
Maxijul etc.





ORAL?

Example:

BREAKFAST:
Raspberry & coconut porridge

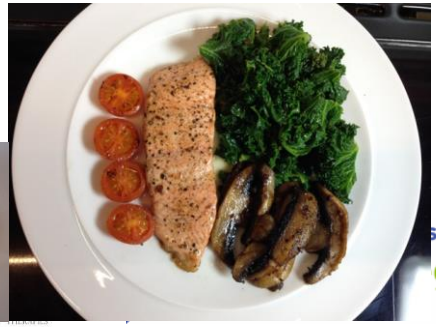


LUNCH:
Spinach watercress
& rocket soup
with Sukrin bread & cheese

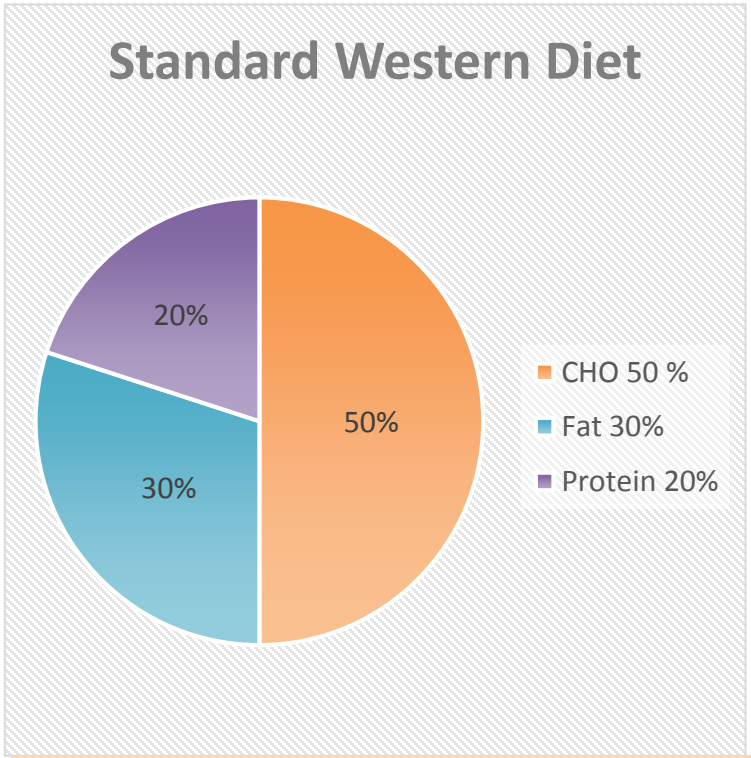


DINNER:
Salmon, mushrooms, kale
& baby tomatoes.
Raspberries and cream



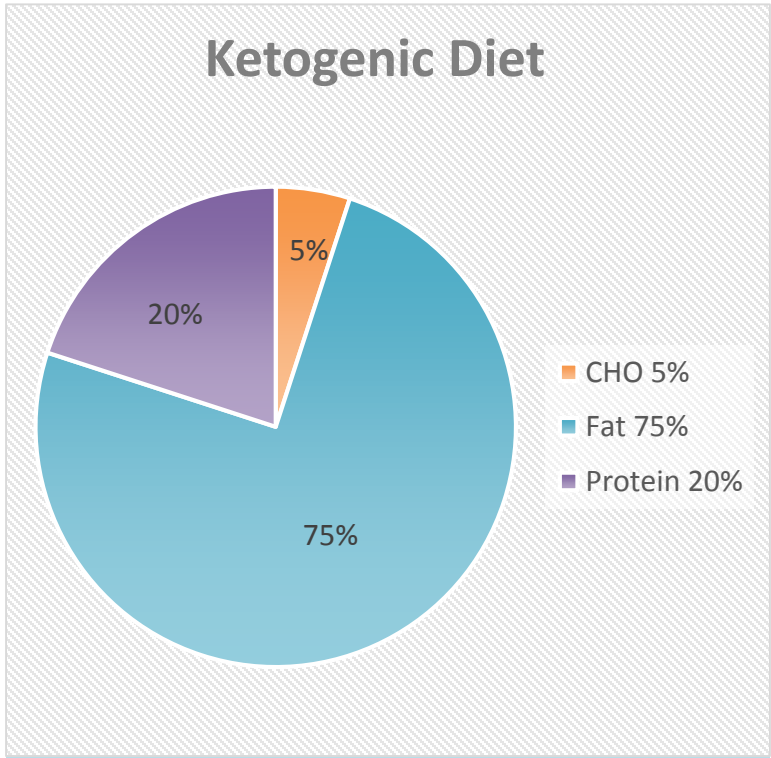


KDT fuel switch: macronutrient profile



1800kcal comes from:

- **225g CHO**
- 60g Fat
- 90g protein



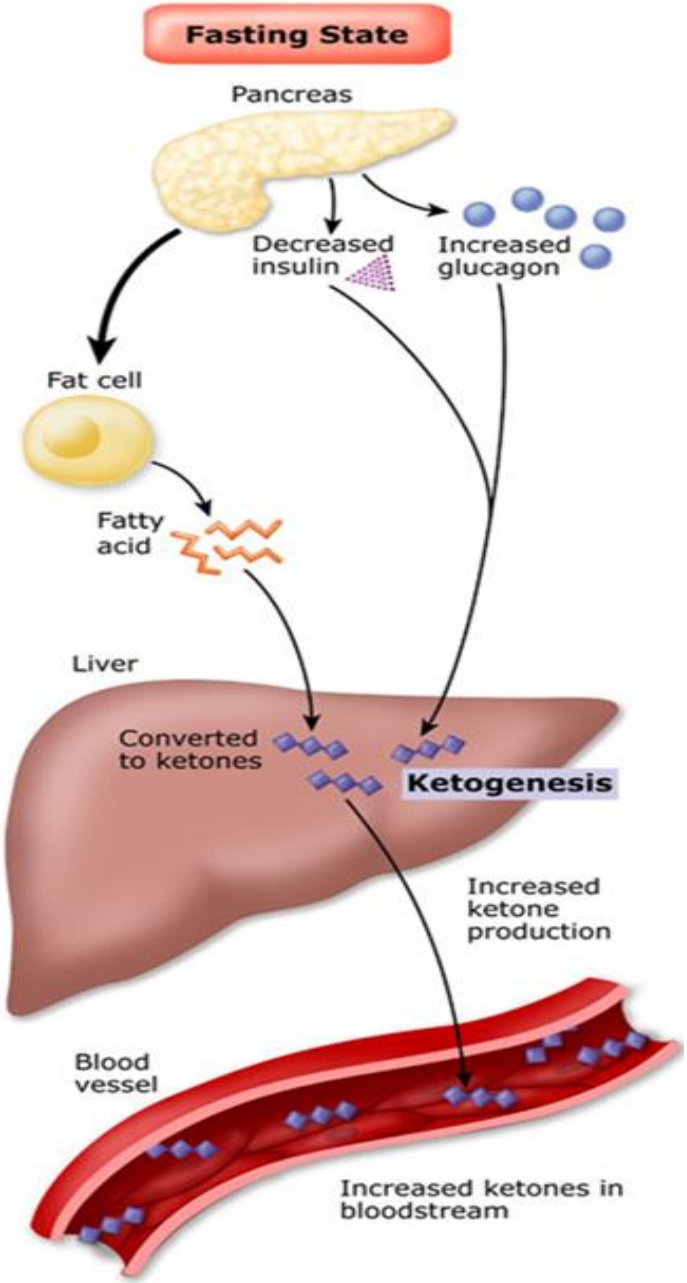
1800kcal comes from:

- 22g CHO
- **150g Fat**
- 90g protein

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The ketogenic ‘shift’ mimics fasting metabolism

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Nutritional Ketosis IS NOT Ketoacidosis?

VERY IMPORTANT DIFFERENCE:

<u>Nutritional ketosis</u> (benign, adaptive state):

- controlled, insulin regulated process
- Blood ketones 1-7mmol/l
- Glucose 3.5-6.5mmol/l ie normal range
- pH in normal range



<u>Ketoacidosis</u> :

- **uncontrolled**
- **lack of insulin**
- **Blood glucose above normal ranges**
- **Blood ketones > 10mmol/l**
- **Acidosis**



HOW DOES KDT WORK IN EPILEPSY?

Multiple mechanisms of action

Possibly different mechanisms in different disorders



Direct:

- **Provision of ketones**
- **Reduced glycolytic flux**

+

Indirect:

- **Mitochondrial biogenesis**
- **Neurotransmitter metabolism**
- **Antioxidant status**
- **Epigenetic modulation**
- **Regulation of inflammation**
- **Alterations in gut microbiome**

- Masino S, Rho JM. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Mechanisms of Ketogenic Diet Action. http://www.ncbi.nlm.nih.gov/books/NBK98219.
- Masino S (Editor).Ketogenic Diet and Metabolic Therapies. 2017 Oxford University Press.
- McDonald TJW, Cervenka MC. The Expanding Role of Ketogenic Diets in Adult Neurological Disorders. Brain Sciences 2018; 8:148

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Old treatment……a new life!

Current Research interest beyond epilepsy:

- Brain tumours & other tumours
- Alzheimer's disease
- Parkinson's disease
- Schizophrenia
- Amylotrophic Lateral Sclerosis (ALS)
- Multiple sclerosis
- Mitochondrial disorders
- Traumatic brain injury / spinal cord injury
- Autism
- Migraine
- Depression
- Aging
- ME/CFS
- Diabetes



Is dysregulation in cellular fuelling a common component linking these conditions ?

The ketogenic diet as a treatment for diverse neurological disorders
Stafstrom CE Rho JM. Frontiers in Pharmacology.
April 2012 Vol3 Article 59

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EPILEPSY EVIDENCE FOR KDT

Ketogenic diets for drug-resistant epilepsy (Review)

Cochrane Library

Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN

2018 Cochrane review : 11 RCTs

- 712 children and adolescents, 66 adults.
- Ketogenic diet for 3 months
- 4 : 1 Classical KD
  - Seizure freedom up to 55%
  - Seizure reduction up to 85%
- Modified Atkins Diet
  - Seizure freedom up to 10%
  - Seizure reduction up to 60%.
- 1 study KD group more alert active and less anxious but no difference in QALY between KD and control group.
- Adverse effects (GI, high cholesterol), short duration, long-term effects unknown.

Conclusion : promising results for use of KD in epilepsy but small no of studies/sample sizes … low overall quality of evidence'

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

Open Access

SPECIAL REPORT

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

[1]Eric H. Kossoff, [2]Beth A. Zupec-Kania, [3]Stéphane Auvin, [4]Karen R. Ballaban-Gil, [5]A.G. Christina Bergqvist, [6]Robyn Blackford, [7]Jeffrey R. Buchhalter, [8]Roberto H. Caraballo, [9]J. Helen Cross, [10]Maria G. Dahlin, [11]Elizabeth J. Donner, [12]Orkide Guzel, [13]Rana S. Jehle, [14]Joerg Klepper, [15]Hoon-Chul Kang, [16]Danielle A. Lambrechts, [17]Y.M. Christiana Liu, [18]Janak K. Nathan, [19]Douglas R. Nordli Jr, [20]Heidi H. Pfeifer, [21]Jong M. Rho, [22]Ingrid E. Scheffer, [23]Suvasini Sharma, [24]Carl E. Stafstrom, [25]Elizabeth A. Thiele, [26]Zahava Turner, [27]Maria M. Vaccarezza, [28]Elles J.T.M. van der Louw, [29]Pierangelo Veggiotti, [30]James W. Wheless, [31]Elaine C. Wirrell, The Charlie Foundation, Matthew's Friends, and the Practice Committee of the Child Neurology Society

Epilepsia Open, 3(2):175–192, 2018
doi: 10.1002/epi4.12225

2018 International Consensus

- **KDT can effectively treat individuals: infants to adults.**
  - <2 years may be ideal age to commence KDT
  - Adult trials & clinical experience suggest KDT outcomes are similar to those in children.
  - Long term use for some conditions - transition to adult care needed.
  - **KDT should be considered earlier than later in drug resistant epilepsy**

2018 Consensus Statement for ketogenic diet therapy: Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open https://onlinelibrary.wiley.com/doi/10.1002/epi4.12225

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Table 1
)

Epilepsy syndromes with response to KDT consistently "better than average"

(>70% gain ≥50% reduction in seizures)

Angelman syndrome

Complex 1 mitochondrial disorders

Dravet syndrome

Epilepsy with myoclonic–atonic seizures (Doose syndrome)

Glucose transporter protein 1 (Glut-1) deficiency syndrome (Glut1DS)

Febrile infection–related epilepsy syndrome (FIRES)

Formula-fed (solely) children or infants

Infantile spasms

Ohtahara syndrome

Pyruvate dehydrogenase deficiency (PDHD)

Super-refractory status epilepticus

Tuberous sclerosis complex

2018 Consensus Statement for ketogenic diet therapy: Epilepsia Open
https://onlinelibrary.wiley.com/doi/10.1002/epi4.12225

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Adverse effects?

- Gastrointestinal symptoms 12-50%
  - majority alleviated with diet modification
- Lethargy , nausea , hypoglycaemia
  - Higher risk if rapid introduction of regime
- Raised total cholesterol
  - Readily settles to baseline in 12 months
  - Often higher HDL / low TG's
  - Adjust fat composition – rare to discontinue.
- Renal calculi (3-7%)
  - Rarely require diet discontinuation
  - Increase fluids & use K^+ Citrate
- Unplanned weight loss / gain
  - Adjust prescription / check being maintained.
- Increase in seizures can occur in some!

Consensus view:

'evaluate risk-benefit of continuation at all times'

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The KD effect on life BETWEEN seizures

- **Reported improvement in QOL; mood, alertness, memory, sleep , and / or attention in 87% (n=48) (Roehl 2018)**
- mental conception is clearer" (Barborka 1930)
- "improved thinking and mood without any reduction in AED's"
- "one patient continued the diet because of improvement in cognition" (Sirven 1999)
- "mood improved in all patients completing the study" (Carrette 2009)
- "the changes in the quality of life were unrelated to the accompanying changes in the frequency of the seizures" (Mosek 2009)
- Weight loss is commonly reported as a side effect of the diet therapy (Kossoff 2008, Carrette 2009, Mosek 2009, Klein 2010, Smith 2011, Roehl 2018).



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STATUS EPILEPTICUS

A neurological and medical emergency

Status Epilepticus

- SE: ≥5 minutes of either continuous seizure activity or repetitive seizures with no intervening recovery of consciousness.
- Refractory SE; Seizures continue despite appropriate first- and second-line AEDs
- Super Refractory SE: If status epilepticus continues or recurs 24 hours or more after the initiation of treatment with anaesthetic agents to induce seizure suppression,

Tanya J. Williams and Mackenzie C. Cervenka.T
The role for ketogenic diets in epilepsy and status epilepticus in adults
Clin Neurophysiol Pract. 2017; 2: 154–160.

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Medical considerations: Adult SE

Absolute Contraindications:

- Abnormalities of fatty acid metabolism
- Porphyria

Acute Contraindications

- Propofol?

Adult specific medical cautions:
History of :

- familial hyperlipidaemia
- renal stones
- eating disorders

No possibility of pregnancy

Caution & manage prior to commencement :

- dysphagia
- gastro-oesophageal reflux
- chronic constipation

Manage prior to diet initiation.

- Type 2 Diabetes ; medication adjustment.
- Type 1 diabetes (Co-work with DMS team?)

2018 Consensus Statement for the ketogenic diet :
Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group
Epilepsia Open https://onlinelibrary.wiley.com/doi/10.1002/epi4.12225

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Refractory SE



Neurocrit Care (2019) 30:652–657
https://doi.org/10.1007/s12028-018-0653-2

NEUROCRITICAL CARE SOCIETY

ORIGINAL ARTICLE

The Feasibility, Safety and Effectiveness of a Ketogenic Diet for Refractory Status Epilepticus in Adults in the Intensive Care Unit

Brandon A. Francis[1*], Jennifer Fillenworth[2], Philip Gorelick[3], Kristina Karanec[2] and Adriana Tanner[2]

- Retrospective study; n=11, 18-80 yrs (mean 48yrs) with RSE treated with a KD treatment algorithm
- Median 3 AED's prescribed before initiating the KD.
- Median 1 day RSE duration before KD (Propofol common delay).
- 90.9% (*n* = 10) of patients achieved ketosis within a median of 1 day.
- RSE resolved in 72.7% (*n* = 8) of patients; however, 27.3% (*n* = 3) developed super-refractory status epilepticus.
- Side effects included metabolic acidosis, hypoglycaemia and hyponatremia. One patient (20%) died.

Conclusions: KD may be feasible, safe and effective for treatment of RSE in the ICU. A randomized controlled trial (RCT) may be indicated to further test the safety and efficacy of KD.

Francis et al. Neurocritical Care (2019) 30:652–657

SRSE: a UK case example.

Male age 19: Lennox Gastaut SE – SRSE

- KD requested at day 79.
- Initiated
  - gradual increase in KD feed ratio over 6 days
  - **significant improvement within 1 week**
  - Able to commence wean from ventilation
- Left ICU on Day 196
- Further 2 months in a neurology ward
- Discharged on ketogenic enteral feed via RIG

Key lessons for ICU staff:
Medics: IV fluids should be carbohydrate free & infections destabilise KD control
Nurses: Feed components must be weighed accurately & feed delivered at correct times.
Pharmacists: All medications should be carbohydrate free.

Ryan H (2019). Ketogenic Diet in Adult Intensive Care. *CN; 19(2): 41-43*

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Adult Status Epilepticus Ketogenic Diet Treatment Protocol

Screen for abnormalities of FA metabolism : urine organic acids / Carnitine profile

Baseline

- Fasting lipid profile, CMP, CBC, selenium, vitamin D, amylase, lipase, urine ketones, +/-beta hCG
- Continuous video EEG monitoring
- Document baseline weight and height

Diet Initiation

- Minimize carbohydrates in medications, parenteral and intravenous fluids
- Dietetic assessment & replace enteral formula with ketogenic liquid formula (reduced calorie provision for 24 hrs?).
- **In UK now have adult feed available : Ketocal 2.5:1LQ (incl. 25% fat as MCT)**

Cervenka et al. Neurology 88(10):2017.

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Adult SE KDT Protocol contd

Diet Maintenance

- Monitor glucose 4 hrly. Give IV dextrose 12.5 gram bolus every 20 minutes if <50 mg/dl
- Check urine acetoacetate, serum β-hydroxybutyrate every 12 hours
- In 48 hours, check CMP (give oral bicarb to maintain serum > 18 mEq/L)
- After 72 hours, wean sedating medications:
  - If unsuccessful, try again at 1 week.
  - If unsuccessful after 2 weeks of KDT, stop diet

Upon Transfer or Discharge

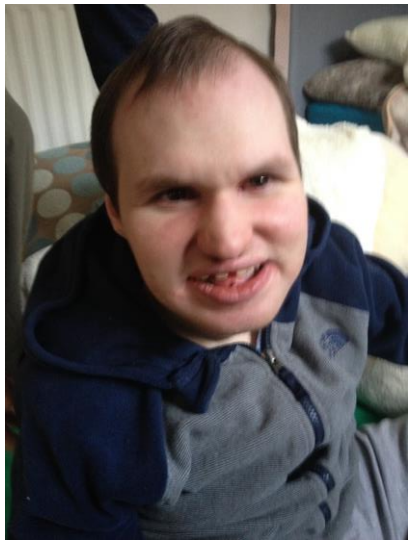
- Continue enteral ketogenic diet OR if patient is taking oral nutrition, begin modified Atkins diet (20 grams per day net carbohydrates, high fat)
- Record urine ketones twice per week, weights weekly, seizures daily
- Follow up in outpatient diet clinic in 1 month, repeat amylase and fasting lipid panel.

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ENTERAL ADULTS WITH DRE

Case example: Matthew 21years



- **Diagnosis: c**omplex syndrome:
  - microcephaly, severe learning disability.
  - Enterally fed (PEG)
  - **14 years of drug resistant epilepsy.**
  - **Medications:** Lacosamide, Gabapentin and Midazolam+++.
  - Tried 7^{+} AED's previously
  - **Monthly Seizure cycle :** absences & tonic clonic seizures, post ictal migraine and self harm: bang head, bite, scream.
  - **March 2017 KDT commenced KDT via enteral feed**

After 14 years…..KDT stopped seizures within one month.

No seizures, no pain, no dribbling, circulation improved, doesn't catch bugs anymore……..relaxed and happy (most of the time)!

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Adult KDT developments in the pipeline?

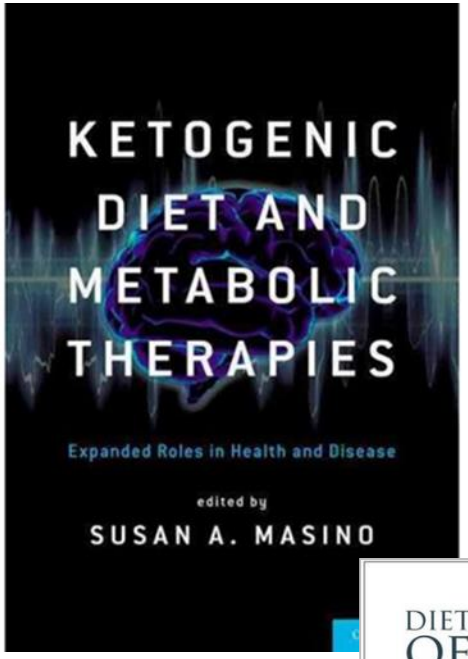
- **UK Adult KDT Trial**
- 10 centres in UK and Ireland: 300 patients.
- Randomised to MKD or 'healthy eating'.
- Enteral feeders accepted too (using Classical 2.5:1 ratio)
- Funding declined Nov. 2018 ….will try again in 2019!

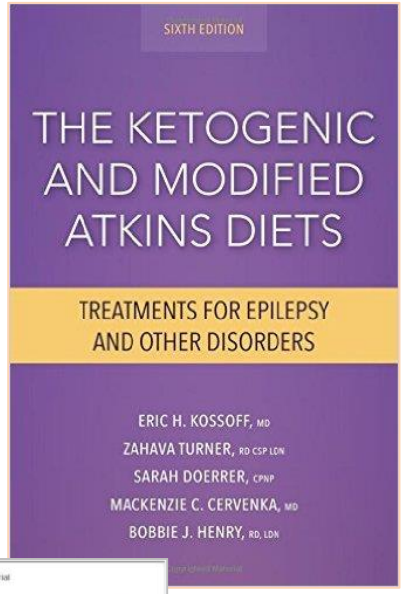
Martin-McGill KJ et al. The modified ketogenic diet for adults with refractory epilepsy: An evaluation of a set up service. Seizure. 2017 Sep 1;52:1-6. Kirsty.Martin@liverpool.ac.uk

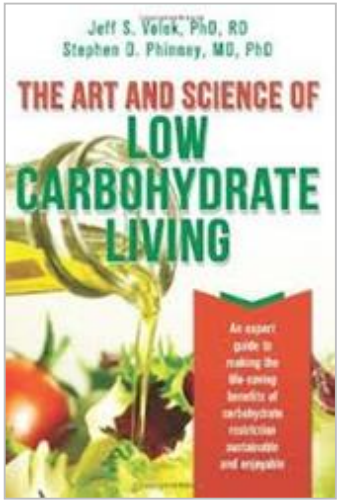
- **International recommendations for the management of adults treated with KDT**
- 20 centres completed the survey.
- Representing KDT Rx in > 2000 adult cases.
- In draft at present – to be published 2020?

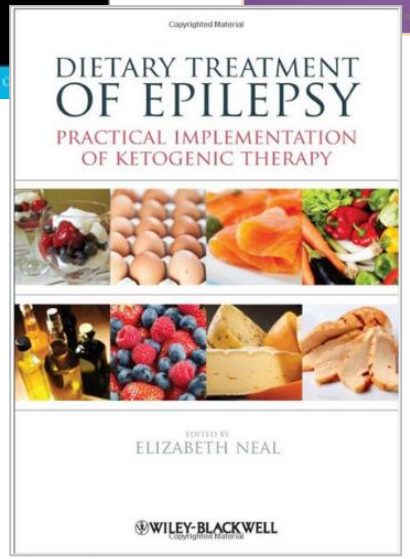
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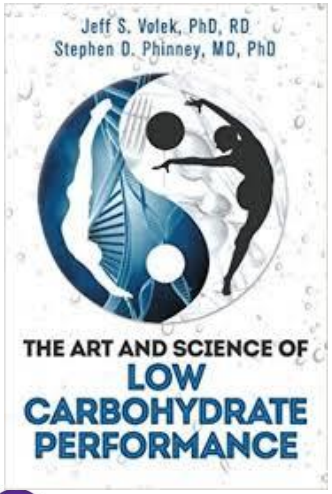
Helpful books: Reference











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Sharing and exploring KDT practice:

Ketogenic Dietitians
Research Network

Aims of the KDRN

- Provide a **support network** for **dietitians** undertaking, or interested in undertaking ketogenic diet (KD)-related **research.**
- **Share practice** and **research** ideas between UK ketogenic centres.
- Seek funded research time for **dietetic-lead projects.**
- Promote **evidence-based practice** by publishing results from our projects, and through sharing and review of relevant journal articles.

Contact Dr Natasha Schoeler : n.schoeler@ ucl.ac.uk

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Summary

- Ketogenic diet therapy can be effective in the management of drug resistant epilepsy in both children and adults.
- Patients & families who **want** to do it **can do it**.
- It requires MDT approach: dietetics & neurology to initiate and monitor to optimise outcomes.
- Consider earlier in SRSE
- Enteral patients with DRE should be offered trial of KDT.
- KDT requires continued research into ;
  - Mechanisms of action – wider application in neuro conditions / neuro rehabilitation.
  - Novel (easier) means of achieving ***the ketogenic effect*** : eg Ketone esters, MCT products etc.

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