Ketogenic Diets for drug-resistant epilepsy

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- Ketogenic diet types
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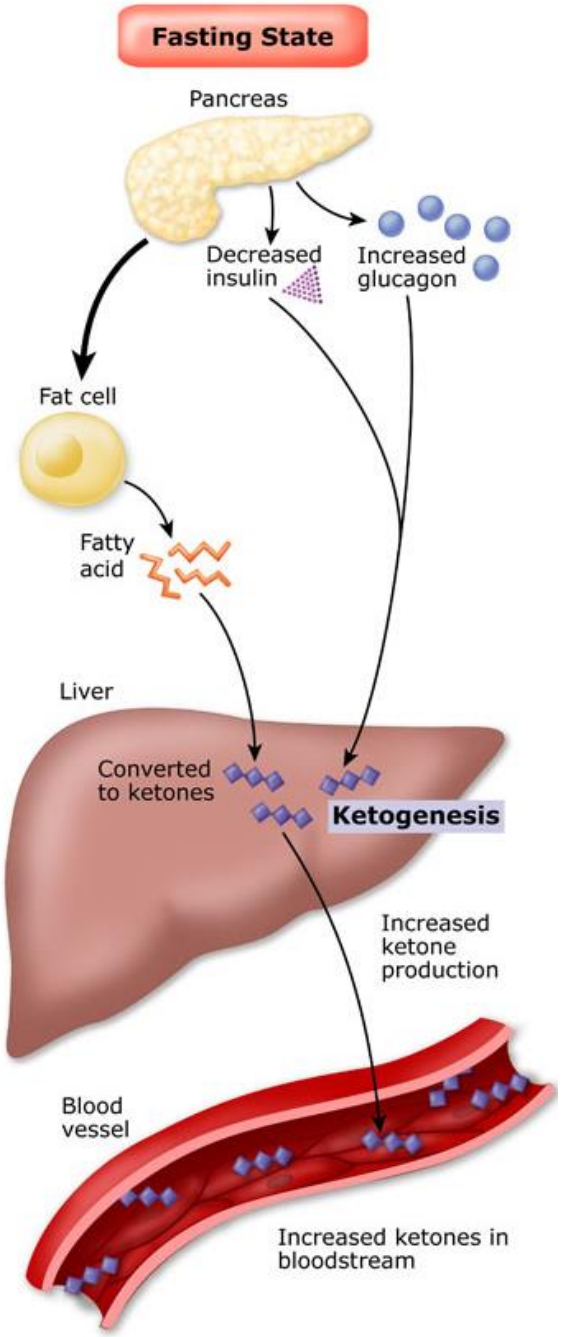
What are ketogenic diets?

A group of high-fat, low-carbohydrate, moderate protein diets, designed to mimic the metabolic effects of starvation



What are ketogenic diets?

Treatment of choice for certain neurometabolic disorders:

- glucose transporter type 1 deficiency syndrome
- pyruvate dehydrogenase complex deficiency

Used in the treatment of epilepsy and other neurological disorders

History of KDs

HIPPOCRATES
Starvation associated with cessation of seizures

MARKS GOSPEL
'prayer and fasting' cured seizures

CONKLIN
'Patient deprived of food…up to 25 days'

WILDER
KD instead of fasting

PETERMAN
10/17 (59%) patients seizure-free

BC

1910

1921

1924

1930s

NBC DATELINE
Resurgence of KD

KOSSOFF
Modified Atkins

NEAL
First RCT

1971

1994

1999

2003

2008

HUTTENLOCHER
MCT KD created

NUTRICIA
First Ketogenic formula produced

NICE GUIDELINES
Advocating use of KD in children with drug-resistant epilepsy in UK

2012

2016

2017

2018

2019

2020

VAN DER LOUW
Guidelines for use of KD in infants

KDRN
Supporting dietetic-led research

KOSSOFF
Optimal clinical guidelines

VAN DER LOUW
Guidelines for KD parenteral nutrition

Types of Ketogenic Diets

Classical ketogenic diet (CKD)

Modified ketogenic diet (MKD)

MCT diet (MCT KD)

Low Glycaemic Index Treatment (LGIT)

Classical ketogenic diet

- Based on ratio of fat to protein and carbohydrate
- All ingredients weighed
- Recipes provided to the family
- Does not usually involve Medium Chain Triglyceride (MCT) fat

MCT ketogenic diet

- Generally household measures for fat, protein and carbohydrate
- MCT measured dose with all foods

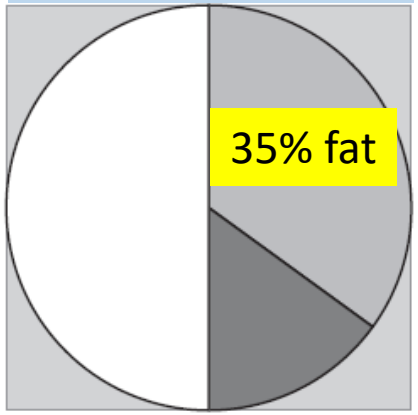
Modified Ketogenic Diets

- Modified Atkins Diet (USA)
- Modified Ketogenic Diet (UK)
- Weighed carbohydrate exchanges (1g, 5g)
- Fat household measurements
- Protein ‘normal’ portions

Low Glycaemic Index Treatment

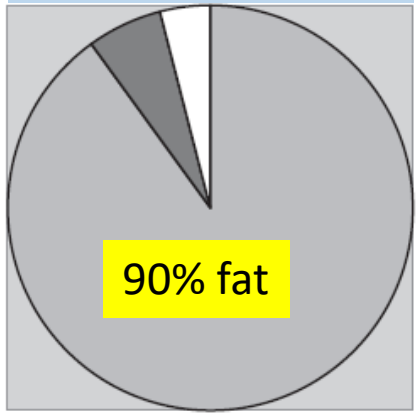
- Rarely used in UK
- 40–60 g/day total carbohydrates
- Low glycaemic index (<50) carbohydrate foods allowed

Western diet



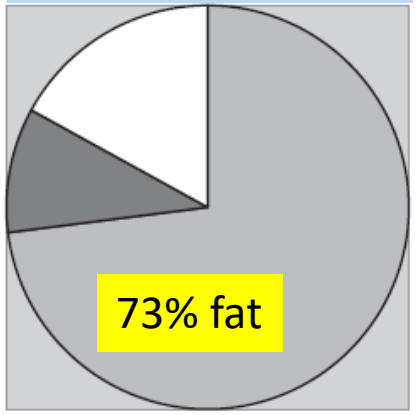
- Fat (35%)
- Protein (15%)
- Carbohydrate (50%)

4:1 classical



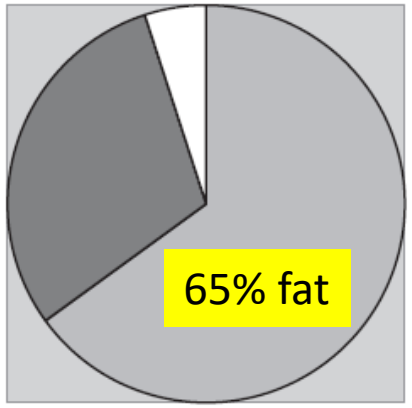
- Fat (90%)
- Protein (6%)
- Carbohydrate (4%)

MCT KD



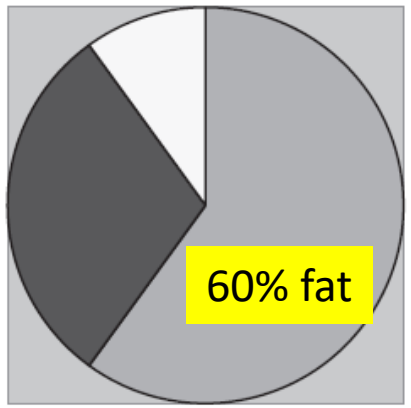
- Fat (73%, including 30-60% MCT)
- Protein (10%)
- Carbohydrate (17%)

Modified Atkins

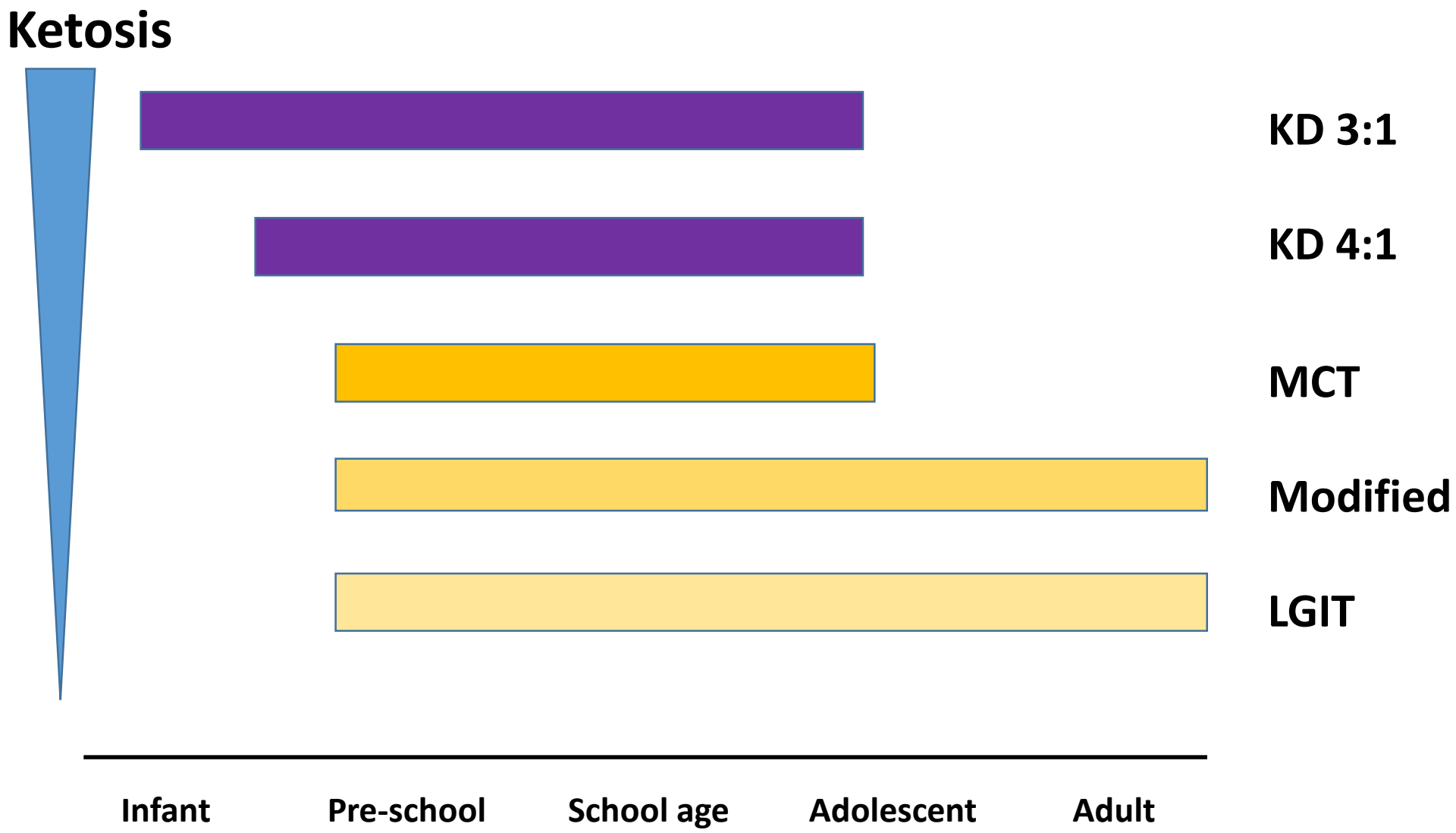


- Fat (65%)
- Protein (30%)
- Carbohydrate (5%)

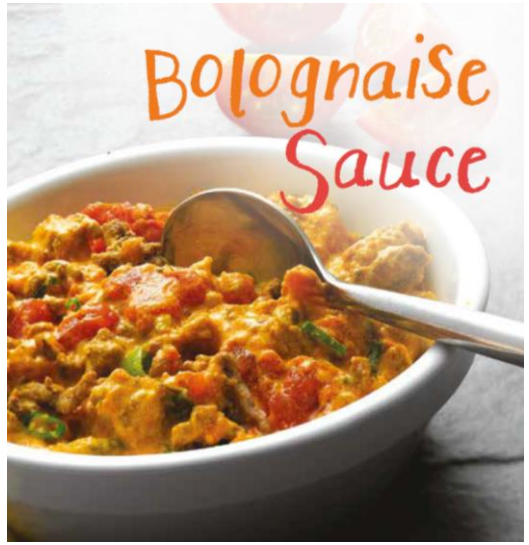
Low GI Treatment



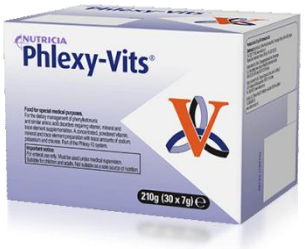
- Fat (60%)
- Protein (30%)
- Carbohydrate (10%)


Ketosis
KD 3:1
KD 4:1
MCT
Modified
LGIT
Infant
Pre-school
School age
Adolescent
Adult

What do ketogenic diets look like?



Ketogenic products



Where is the Ketogenic Diet Used in the World?

Kossoff and McGrogan, 2005. Worldwide use of the ketogenic diet

Treatment indications/contraindications

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

Table 3. Contraindications to the use of KDT

Absolute

- Carnitine deficiency (primary)
- Carnitine palmitoyltransferase (CPT) I or II deficiency
- Carnitine translocase deficiency
- β-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

Relative

- 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)

Cochrane Library

Cochrane Database of Systematic Reviews

Ketogenic diet for epilepsy (Review)

Levy R, Cooper P

This record should be cited as:
Levy R, Cooper P. Ketogenic diet for epilepsy. *Cochrane Database of Systematic*
10.1002/14651858.CD001903.

2003: No Randomised controlled trials

Modified Atkins Diet

Up to 25% seizure-free

Up to 60% ≥50% seizure reduction

Classical 4:1

Up to 55% seizure-free

Up to 85% ≥50% seizure reduction

Ketogenic diets for drug-resistant epilepsy (Review)

Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN.
Ketogenic diets for drug-resistant epilepsy.
Cochrane Database of Systematic Reviews 2018, Issue 11. Art. No.: CD001903.
DOI: 10.1002/14651858.CD001903.pub4.

2018: 11 Randomised Controlled Trials, 15 publications, including 1 for adults

Side effects:
Short-term and manageable

	Constipation incidence %	Vomiting incidence %	Diarrhoea incidence %
Neal 2008 Classical/MCT	**33%**	**24%**	**13%**
Sharma 2013 MAD	**46%**	**10%**	**0%**
Cai 2017 Review	**13%**	**10%**	**4%**

Side effects:
Short-term and manageable

Other:
-Lethargy
-Irritability
-Hunger
-Loss of appetite
-Respiratory tract infection
-Exacerbation of gastro-oesophageal reflux – medical management

‘Fairly consistent across different dietary interventions’

(Martin-McGill et al 2018)

Side effects:
Short-term and potentially serious

Hypoglycemia and excess ketosis

Incidence	1.8%	3.1%

(Cai et al 2017)

Longer-term side effects

Side effect	Early/Late	Reported incidence %
Hyperlipidaemia	Early/Late	4.6 - 14.7
Osteopenia	Late	1.2 - 14.7
Renal stones	Late	1.3 - 3.1
Cardiomyopathy	Late	0.8
Pancreatitis	Early/Late	0.1 - 0.8
Reduced plasma zinc	Early/Late	0.4
Bruising	Early/Late	0.3
Fatty liver	Early/Late	0.1
Pica	Early/Late	0.07

(Wheless 2001; Keene et al 2006; Kang et al 2004; Cai et al 2017)

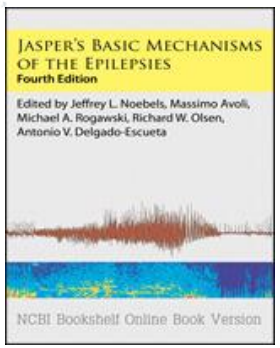
Home monitoring

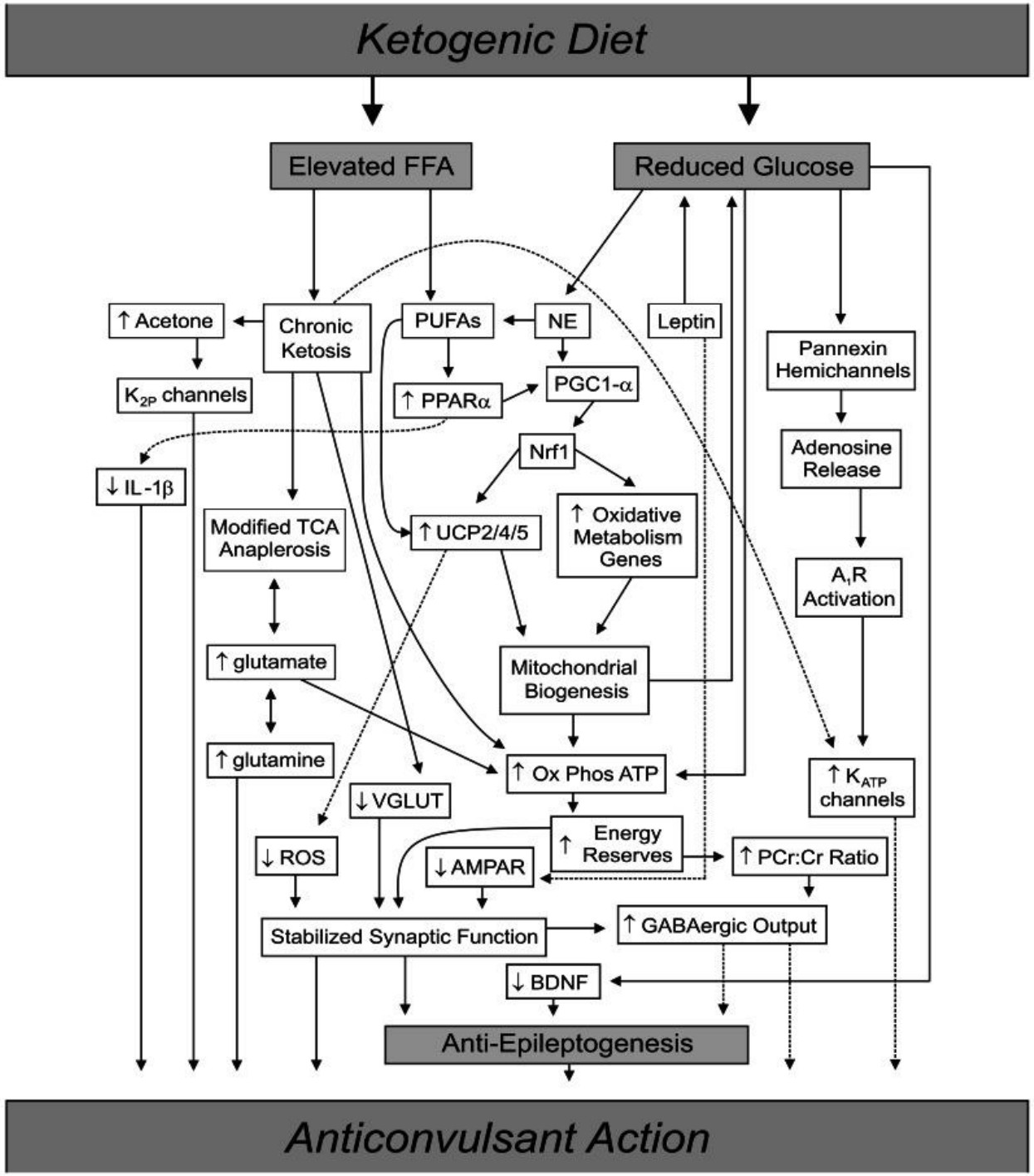
- ketones/glucose
- weight
- seizures

Hospital monitoring

- biochemistry
- growth
- other (ultrasound, DEXA…)

How does it work?



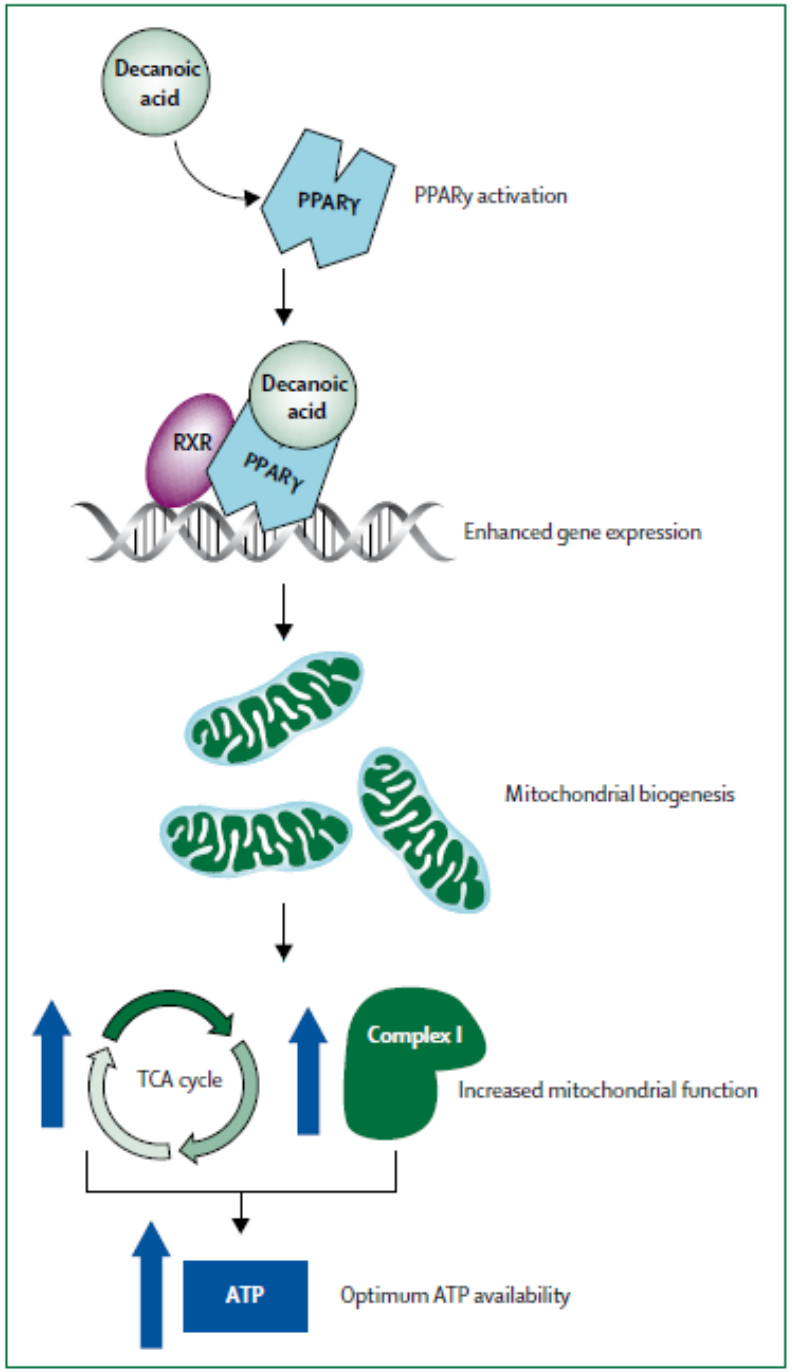


Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders

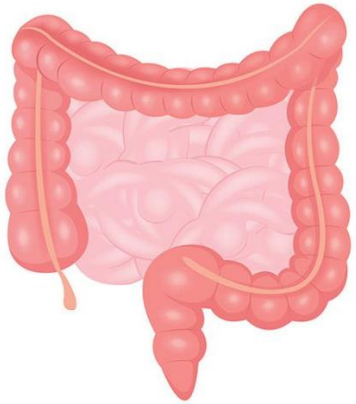
Katrin Augustin, Aziza Khabbush, Sophie Williams, Simon Eaton, Michael Orford, J Helen Cross, Simon J R Heales, Matthew C Walker*, Robin S B Williams**

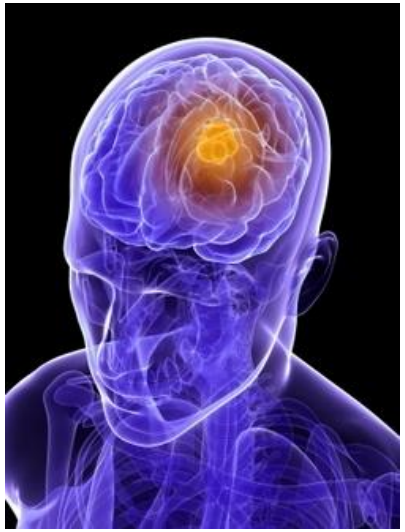
Lancet Neurol 2018; 17: 84–93

- Medium-chain triglycerides (containing decanoic acid and octanoic acid) are consumed as part of the medium-chain triglyceride ketogenic diet
- Medium-chain fatty acids (decanoic acid and octanoic acid) are liberated from triglycerides in the intestine and transferred to the liver, where most of these medium-chain fatty acids are broken down to three ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone)
- Both free fatty acids and ketones are transported to the brain through blood circulation
- Fatty acids and ketones are transported across the blood–brain barrier, where they are available as a source of energy to brain cells



Current research trends





Conclusions

- KDs are an effective treatment for epilepsy
- Palatable and flexible
- Medically managed
- Further research needed

Acknowledgements

- Prof Helen Cross (UCL Great Ormond Street Institute of Child Health, GOSH)
- Zoe Simpson (GOSH)

NIHR | Great Ormond Street Hospital Biomedical Research Centre

Ketogenic Dietitians Research Network

Further Reading

- Matthew's Friend – charity https://www.matthewsfriends.org/
- The Daisy Garland – charity https://www.thedaisygarland.org.uk/
- Charlie Foundation – charity https://charliefoundation.org/
- *Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group*. Epilepsia Open, 3(2):175–192, 2018 doi: 0.1002/epi4.12225.
- *Ketogenic diet guidelines for infants with refractory epilepsy*. Eur J Paediatr Neurol. 2016 Nov;20(6):798-809. doi: 0.1016/j.ejpn.2016.07.009.
- *Role of Ketogenic Diets in Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease).* Nutrients. 2019 Jan; 11(1): 169. doi: 0.3390/nu11010169.
- *The Ketogenic Diet as a Treatment Paradigm for Diverse Neurological Disorders*. Front Pharmacol. 2012; 3: 59. doi: 10.3389/fphar.2012.00059

References

- Martin-McGill et al 2018. doi: 10.1002/14651858.CD001903.pub4
- Cai et al 2017. doi: 10.1007/s12519-017-0053-2
- Keene et al 2006. doi:10.1016/j.pediatrneurol.2006.01.005
- Kang et al 2004. doi: 10.1111/j.0013-9580.2004.10004.x
- Wheless 2001. doi: 10.1177/08830738010160090l
- Borges 2008. doi: 10.1111/j.1528-1167.2008.01838.x
- Mechanisms of Ketogenic Diet Action. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Noebels JL, Avoli M, Rogawski MA, et al., editors. Bethesda (MD): National Center for Biotechnology Information (US); 2012.