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KETOGENIC DIET: ONE HUNDRED YEARS AND STILL GOING STRONG

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After a century of clinical use in epilepsy management, you might have thought by now that the ketogenic diet (KD) would have been superseded and politely slid way into obscurity. To the contrary, scientific interest in KD is increasing. Here, Susan Wood examines how KDs work and what impact they have on neuro disorders.

In the drug-resistant epilepsy sector, KD milestones are now emerging more quickly than ever (see Figure 1). In the last five years alone, internationally agreed recommendations for the optimal clinical management of children receiving dietary therapies for epilepsy have been expanded and updated,[1] and new publications focusing on infants,[2] parenteral nutrition[3] and adults[4] are now available to guide on clinical use.

In October 2021, at the 7th Global Symposium on Medical Ketogenic Therapies (www.globalketo.com) the International Neurological Ketogenic Society (INKS - www.globalketo.com/inks) will be launched to drive this incredibly versatile metabolism-based therapy into its second century.

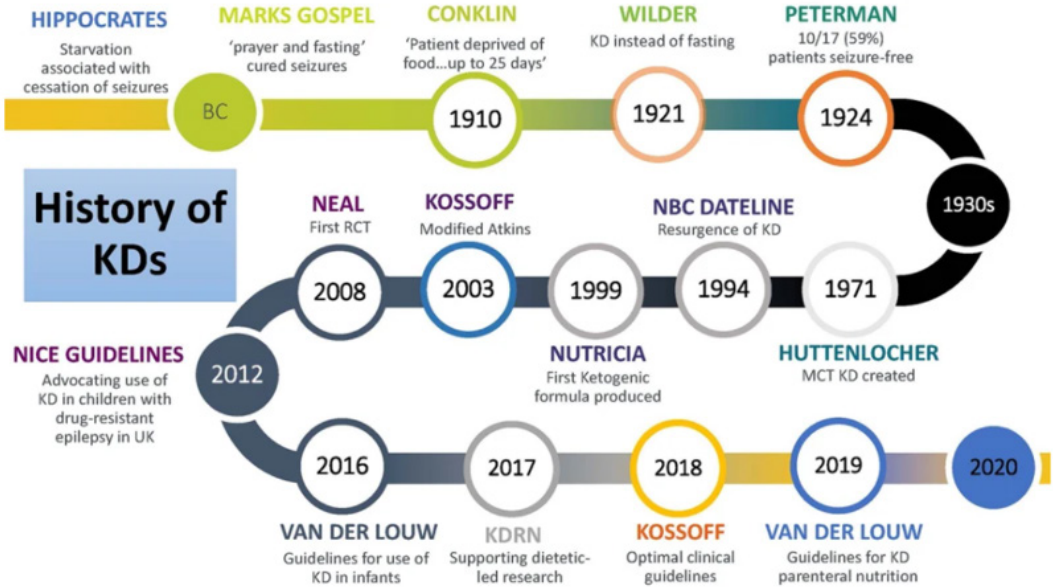
KETOGENIC DIET THERAPY (KDT) BASICS

KDT is an evolving journey, with symptom management being the target destination. The degree of ketosis does not necessarily define the outcome and optimal levels will vary from one individual to another. Medical KD's share common base dietary principles in that they are low in carbohydrate, high in fat and provide adequate protein (a high protein intake will impair ketogenesis).

KD protocol selection is based on age, medical, nutritional and lifestyle needs of the individual. All are recommended to include medical screening, dietetic assessment, prescription planning, KDT education, home monitoring and frequent dialogue between the patient and supporting KDT team to enable adjustments and optimal navigation along the way. This enables adverse effects, such as constipation or unplanned weight changes, to be picked up and managed promptly. In the case of epilepsy management, an assessment of efficacy can generally be made after three to four months of optimally monitored and individually adjusted KDT.

KD protocols differ in their method of controlling the delivery of macronutrients and energy across meals.[5] The emergence of more liberal KDT protocols such as the Modified Atkins Diet,[6] and variations such as the Modified Ketogenic Diet used in the UK,[7] has opened up KDT as a more practical option for adults. These diets focus primarily on strict control of carbohydrate in meals while encouraging generous amounts of fats to appetite and moderate portions of protein. Medium-chain triglyceride (MCT)

Figure 1: A condensed history of the ketogenic diet as epilepsy treatment



Graphic courtesy Natasha Schoeler RD PhD

oil can also be incorporated into these protocols to enhance ketogenesis if required during the fine-tuning process.

SO HOW DOES A KD WORK?

When the body goes from the fed to the fasted state, the liver switches from an organ of carbohydrate utilisation and fatty acid synthesis to one of fatty acid oxidation and ketone body production. Ketones are circulated as an alternative energy source to glucose, ensuring uninterrupted fuelling of essential tissues with high energy demand (eg, brain and heart muscle).[8] A low carbohydrate KD (usually below 25g carbohydrate per day) mimics this fasting state and shifts us into fat burning mode, using fats consumed in the diet, supplemented with fats taken from body stores if the dietary fat intake is insufficient.[6] It results in a sustained presence of ketones (blood β-hydroxybutyrate >0.5-5mmol/l) and a flattening of post-meal glucose and insulin peaks, with levels tending toward the mid to lower end of the normal ranges. This benign nutritional ketosis associated with a low carbohydrate KD is an insulin/glucagon regulated process and must not be confused with diabetic ketoacidosis, resulting from inadequate insulin secretion.

One hundred years on from its first use as a treatment for epilepsy, scientists still struggle to pin down the mechanism/s responsible for 'the ketogenic effect'. Evidenced effects to date, are as follows:[9]

Direct effects

- Providing ketones as an additional fuel source and reducing fluctuations in blood glucose levels

Indirect effects

- Epigenetic modulation (β-hydroxybutyrate is an endogenous inhibitor of histone deacetylases)
- Increasing mitochondrial number in brain tissue (mitochondrial biogenesis)
- Altering neurotransmitter metabolism
- Altering antioxidant status
- Regulation of inflammation
- Alterations in the gut microbiome[10]

So, it turns out that ketones are more than simply an alternative to glucose in cellular metabolism. Over time, ketogenic adaption drives a myriad of biochemical pathway changes, enhances cellular metabolism, regulates inflammation, and can protect neurological

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600K

people in the UK diagnosed with epilepsy and receiving anti-epileptic drug (AED) treatment; that's 1 in every 103 people[1]

36%

Epilepsy patients have inadequate control of seizures with AEDs[2]

Drug Resistant Epilepsy

Failure of two or more appropriately chosen AEDs to achieve seizure freedom[2]

AED side effects

commonly associated with drowsiness, blurred vision, dizziness, nausea and vomiting[3]

Increased risks

- Injury
- SUDEP
- Hospital visits
- Depression and anxiety
- Developmental issues[4]

Ketogenic Diet Therapies

50%

chance of reducing seizures[6]

More palatable than ever before

Candidates for Ketogenic Diet Therapies[5]

- Angelman syndrome
- Complex 1 mitochondrial disorders
- Dravet syndrome
- Epilepsy with myoclonic-atonic seizures (Doose syndrome)
- Glucose transporter protein 1 (Glut-1) deficiency syndrome
- 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
- The failure of 2 or more **AEDs**

This information is intended for healthcare professionals only.

The Ketocal range are Foods for Special Medical Purposes for the dietary management of drug resistant epilepsy or other conditions where the ketogenic diet is indicated and must be used under medical supervision.

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DRUG RESISTANT EPILEPSY

Medication is not always the answer.

Table 1: Ketogenic therapy; emerging neurological applications/future potential

Brain tumours	Traumatic brain injury
Alzheimer's disease	Post-stroke care
Parkinson's disease	Autism
Amylotrophic Lateral Sclerosis (ALS)	Migraine and cluster headaches
Multiple sclerosis	Schizophrenia
Mitochondrial disorders	Depression / Anxiety

function.[11] It is for this reason that the therapeutic potential of KD is being considered for the prevention and/or the management of a wide range of conditions, many affecting adults (see Table 1). In the majority of these, metabolic dysregulation and inflammation are considered to play an important part in the pathology.[12]

CAN KDT KNOWLEDGE AND PRACTICE IN EPILEPSY TRANSLATE TO USE FOR OTHER NEUROLOGICAL CONDITIONS?

Yes, it likely can, but each neurological condition will require its own optimised KDT protocol, with an understanding of when, how and for whom this may (or may not) be applied.

For some time, there has been immense interest in finding novel methods of replicating the ketogenic diet 'effect' by simpler means. This seems even more pertinent when therapeutic use in conditions such as Parkinson's disease (PD) or Alzheimer's disease (ALZ) is being considered. Medium-chain triglycerides (C8, octanoic acid and C10 decanoic acid) have a long-established history of use in KD protocols for epilepsy management and there is interest in combining MCT supplementation with time-restricted eating and/or less stringent carbohydrate control in the management of mild cognitive impairment and early ALZ.[13]

More recent 'novel' arrivals, ketone esters and ketone salts, have yet to be evaluated for use in clinical protocols.[14] Certainly, the prospect of achieving 'ketogenic diet in a pill' is nowhere on the horizon at present. In the meantime, with a lack of KD knowledge and expertise in the adult neuro sector and little sign of clinical developments in KD heading their way, patients and their loved ones read the research for themselves and make up their own minds about exploring KD. Most are realistic about their expectations, looking to enhance the effect of their existing medical treatments and improve quality of life through symptom control and enhanced wellbeing. Let me introduce two such adults to you, one with PD, the other with Glioblastoma Multiforme (GBM).

Audrey is 61 and was diagnosed with Idiopathic Young Onset PD at age 59 years. She explains why she is pursuing KD:

"As neurodegenerative disease is often characterised by brain glucose hypometabolism, I thought it might be an idea to try an alternative fuel. I looked at the clinical trials and other research data and it was compelling if not conclusive, however I feel evidence is mounting. At any rate I don't have time on my side (having recently had PD diagnosis) and decided I wouldn't have anything to lose by trying to spend more time in ketosis via diet, intermittent fasting, exercise and supplementing MCT oil and ketone esters when required. I kitted myself out with a ketone monitor to keep a check on levels and sought advice from professionals, so I could adjust my management regime to attain a therapeutic level of ketones of around 1-1.5mmol/l. I also used a continuous glucose monitor too, to find out which foods caused an excessive blood glucose spike and tried to tailor my diet accordingly. An interesting n=1 experiment. As a result, I notice energy levels and mood are vastly improved (I've begun dancing again) and I'm actually not on any PD meds at the moment. I feel memory is better when generating a decent level of ketones. I would like to think that this may delay disease progression. I feel everyone who is diagnosed with a neuro condition should be offered this treatment option early on."

PD is characterised by the progressive death of brain dopaminergic neurons caused by mitochondrial dysfunction. Ketones could provide a fuel source for these at-risk neurons; alternatively, the ketone induced enhancement

of mitochondrial function may protect cells against insults that demand a high energy supply. A recent randomised-controlled pilot trial compared low-fat and KD interventions in PD.[15] They demonstrated that both interventions are feasible and safe and both diets improved the MDS Unified Parkinson's Disease Rating Score. Interestingly, KD-treated patients showed a greater improvement of non-motor symptoms, which are less responsive to L-DOPA treatment and considered the most disabling symptoms of PD.

Paul was diagnosed with Glioblastoma multiforme in 2021 aged 25 years. The following is written by his mum, after discussion with Paul and with his agreement.

"At the beginning, when Paul was still recovering from surgery, we came across the ketogenic diet as a treatment that had potential to work well alongside conventional treatments. There seemed to be research to back this up. My daughter spent ages trying to find a UK dietitian who could help. At first there was opposition, criticism and a lack of awareness of KD from the GP and oncologist. However, following an explanatory letter from a ketogenic dietitian with links to research evidence, coupled with how well Paul is doing, the oncologist is now respectful and supportive of our choice to follow the ketogenic diet.

*"**The positives:** Paul feels well, with mental clarity and increased physical energy and has had no seizures since the first week post-surgery. He is managing chemo with only mild and manageable side effects (slight nausea and mild fatigue) and there has been no need for dexamethasone to reduce brain swelling. It gives a sense of hope, and that there is something that we can do ourselves to help enhance wellbeing and also (hopefully) treatment outcomes. Paul is now claiming the diet as his own, choosing recipes, cooking them, counting carbs, adding fats, monitoring ketones, etc.*

*"**The negatives:** When we started out, we had no dietetic support, but we instinctively felt that diet was an important part of Paul's treatment and so had to find it ourselves. Paul had a team of friends and family to help; others don't have this and would benefit from it. There was a lot of frustrating time spent in the kitchen at first, learning how to manage a new diet and incorporating the diet into family meals was difficult, until we found keto-friendly recipes that worked for the whole family. Paul initially did not like the thought of 'no junk food'. The initial keto flu which lasted about a week was painful and unpleasant. It also came whilst still recovering from craniotomy which exacerbated the symptoms. The cost of glucose and ketone strips for monitoring is high. Self-discipline is required and it can be difficult in the midst of treatment. There is no instant gratification/comfort at being able to eat whatever you like."*

There has been growing interest in the use of KDT in brain tumour management. Those living with brain tumours readily struggle with quality-of-life impairing symptoms such as seizures, fatigue, depression and cognitive impairment, due to both the disease and treatment side effects.

Pre-clinical studies suggest that KDT may sensitise tumours (models of GBM) to chemo-radiation,[16] and published case reports and case series indicate tolerability, safety and direct tumour effects in some.[17] From 2011-2018, Matthew's Friends, (supported by Astro Brain Tumour Fund) provided a charitable clinical KDT support service for adults with brain tumours seeking this option. KDT readily improved seizure management, alleviated chronic fatigue and delivered a sense of empowerment and control to those who chose this approach.[18] Molecular studies and controlled trials are required to understand the impact of KDT as adjuvant therapy, on progression free survival if any, and how best it should be applied.

END NOTE

When I first entered the world of ketogenic therapies for adults, I had to seriously challenge my preconceived and unfounded negative views on low-carbohydrate / high-fat diets. I am so glad I did, as I have found ketogenic therapies to be the most rewarding chapter in my 39 years of dietetics and have never looked back! Adult ketogenic services remain very limited and as a result, many patients like those mentioned above have no choice but to set out alone. Each adult dietitian who takes an interest and is willing to learn about ketogenic therapies, can make a such a difference.

For further background information on medical ketogenic therapies and the annual UK-based Ketocollege training course please see www.matthewsfriends.org, www.kdrn.co.uk (Ketogenic Dietitians Research Network) and www.mfclinics.com/keto-college/.

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Questions relating to: *Ketogenic diet: one hundred years and still going strong*
Type your answers below, download and save or print for your records, or print and complete by hand.

Q.1	Give the common principles of a ketogenic diet (KD).
A	
Q.2	What are ketones?
A	
Q.3	Describe how a low-carbohydrate KD impacts on the body.
A	
Q.4	How is KD protocol selected for an individual?
A	
Q.5	Describe three indirect effects of ketogenic treatment in epilepsy.
A	
Q.6	How can a KD intervention help with those suffering from Parkinson's disease (PD)?
A	
Q.7	Why is KDT being considered for brain tumour management?
A	

Please type additional notes here.