KETOGENIC THERAPY FOR ADULTS WITH DRUG RESISTANT EPILEPSY: TIME IT WAS ON THE MENU FOR ADULTS

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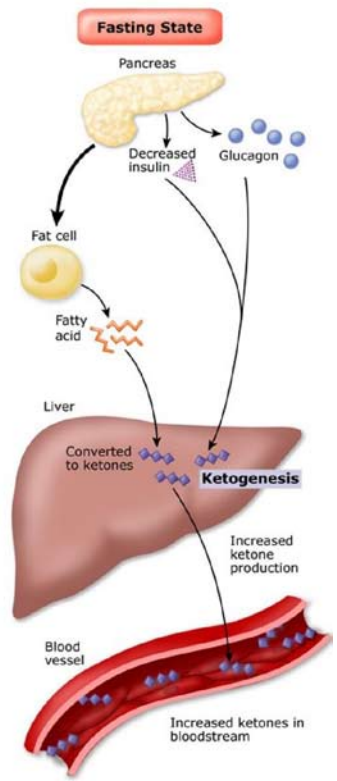
Despite the best efforts of modern anticonvulsant medicines and the availability of novel approaches, such as vagal nerve stimulation and epilepsy surgery, around 30 percent of children and adults are refractory to treatment, enduring a life of poor seizure control and impaired quality of life. The ketogenic diet (KD) has been used as a treatment for epilepsy since the 1920s, pre-dating most anticonvulsant drugs.

It evolved from the knowledge that extended fasting readily led to a significant seizure improvement and that this effect could be replicated by altering the macronutrient profile of the diet, triggering a metabolic shift away from carbohydrate to fat as the predominant dietary energy source.

It was not until 2008 that the first randomised controlled trial (RCT) of KDs in children was published by a pioneering team from Great Ormond Street Hospital, proving efficacy equivalent to modern anticonvulsant drugs and endorsing the use by specialist paediatric teams across the world (1).

The first and largest ever study of KDs in adults (n=81) was published in America in 1930 (2), but despite positive results (over half achieved a 50 percent or greater reduction in seizures) and further small trials over the decades, they continue to be rarely used within the adult epilepsy world. A recent meta-analysis of 12 relevant adult trials (270 adults) reported efficacy in 42 percent of cases, suggesting parity with paediatric trials (3). Almost half of these studies used a modified Atkins diet (MAD); a more liberal approach first used in children in 2003 (4), making treatment a more practical possibility for adults and children alike. A UK adult trial is in the early planning stages and results from a Norwegian RCT started in 2011 are eagerly awaited (5).

Figure 1: Ketone production by liver during fasting conditions (Ketosis)



Credit: The Regents of the University of California

HOW DOES A KETOGENIC DIET WORK?

(See Figure 1). Carbohydrate reduction, the cornerstone of ketogenic diets, reduces glucose availability and the stimulus for insulin secretion. This triggers an increase in the rate of fatty acid oxidation in the liver and the release of

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ketones into the circulation. Brain tissue rapidly adapts to this altered state, using ketones as the primary fuel to drive energy metabolism. The exact mechanisms by which a ketogenic diet exerts its anticonvulsant effect are likely varied and as yet unconfirmed, but it is thought that it enhances brain energy reserves, stabilising neuronal tissue and influences the balance of neurotransmitters and a range of compounds involved in exciting and inhibiting electrical activity within brain tissue (6).

WHAT CHANGES CAN IT DELIVER?

Ketogenic therapy can deliver a significant reduction in seizure frequency, intensity and reduce the time needed to recover from seizures. Adult responders often report more subjective changes, such as being able to think more clearly, concentrate better, have more energy and feel generally brighter in mood (7). Overweight individuals successfully lose weight, reporting positive changes in body shape; particularly waist circumference. These changes readily occur within the first three months of KD treatment, despite there being no change in the anticonvulsant doses. Considering that those referred into ketogenic therapy may have failed for decades to gain adequate seizure symptom control from all available medications, you may appreciate how exciting it is to the patient, the carers and the ketogenic team, when it delivers a life-changing response.

THE DIET PRESCRIPTION

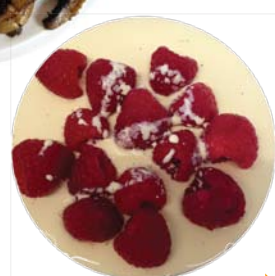
All ketogenic regimes are designed around the nutritional requirements of the individual and are low in carbohydrate, high in fat and provide adequate protein. Traditional ketogenic approaches require weighing of all food items so that ratios (the Classical KD) or percentages (the Medium Chain Triglyceride KD) of fat protein and carbohydrate are maintained consistently in all meals and snacks. However, for the majority of UK adults, we use a more liberal modified ketogenic approach based on the Modified Atkins Diet (MAD) devised by the team at Johns Hopkins Hospital (8).

The basic essentials of a Modified Ketogenic Diet used at Matthew's Friends Clinics are as follows:

What does a ketogenic meal look like?
Three meals providing 6gCHO & 60g Fat:

1 Coconut & raspberry porridge

2 Watercress soup, Sukrin bread and cheese.



3 Pan fried salmon, kale and mushrooms plus raspberries and double cream

- Carbohydrate is restricted to 5.0-10g per meal and 2.0-3.0g in snacks (a total of 20-30g per day) and is always accompanied by fat. A 1.0g carbohydrate exchange system is used and foods are weighed on gram scales. Typical carbohydrate sources are non-starchy vegetables, fruits (mainly berries), nuts, seeds and double cream.
- Fat must always be consumed alongside any carbohydrate containing food. Portion guidance is based on a 10g exchange system and designed to meet individual calorie requirements. For example a 2,000kcal regime will likely require a minimum of 170g fat. Typical fat sources are olive oil, butter, double cream and mayonnaise, with supplementary amounts provided from dietary protein sources.

Figure 2: Treatment criteria and treatment stages

Criteria for ketogenic therapy in adults

The adult will have failed to respond to at least two anticonvulsant medications and be keen to explore the KD.

Medical contraindications (biochemical screening is essential):

- Fatty acid oxidation defects, organic acidurias, pyruvate carboxylase deficiency, any disorders requiring a high carbohydrate treatment.
- A history of familial hyperlipidaemia, renal stones or eating disorders.
- Pregnancy or planning pregnancy.
- Proceed with caution and optimise management before initiating KD therapy: dysphagia, gastro-oesophageal reflux, chronic constipation or diabetes.

Summary of treatment stages

Pre-KD diet assessment appointment; neurologist and dietitian

- Review of epilepsy history, medical management and all relevant tests including biochemical screening.
- Discussion of the practical issues (the food, importance of monitoring), possible negative side effects (mainly lethargy during initial week of transition and constipation. Increased risk of renal stones and osteoporosis long term) and possible outcomes.
- Timing of the treatment to enable commitment to three months with no planned interruptions.

KD treatment education session; dietitian and ketogenic diet assistant

- KD prescription based on BMI, activity levels, estimated energy requirements and whether weight maintenance or loss are desired.
- Guidance on sources of protein CHO and fat.
- Practical menu guidance based on food preferences and lifestyle.
- Guidance on monitoring: blood ketone (1.0-5.0mmol/l) and glucose testing or urine ketone testing as appropriate, seizure, symptom and weight monitoring.
- Guidance on vitamin and mineral supplementation; in most cases, a one-a-day adult multivitamin and mineral, plus additional calcium and vitamin D.

Follow up; dietitian and ketogenic diet assistant

- Regular contact by phone/email; generally once or twice a week until a level of stability is reached.
- Adjust diet prescription as required, based on seizure symptoms, weight and blood or urine ketones.

Three-month follow up; neurologist and dietitian

- Repeat blood biochemistry.
- If no change in seizure pattern or any related parameters (energy levels, alertness, clarity of mind, seizure recovery time etc), consider weaning back towards mainstream low GL diet.
- If proving beneficial, continue treatment and review in a further three months and thereafter six monthly.

At two years, discuss the possibility of weaning back towards a more mainstream low GL diet regime. However, if it is working well for them, adults are reluctant to make significant changes.

Adults seeking advice from their neurology teams are readily told that ketogenic therapy is too complex, unpleasant, unhealthy and only effective in children.

- Protein is consumed with each meal and in normal portions (a therapeutic ketogenic diet is not a high protein diet). Typical protein sources are eggs, poultry, red meat, fish, cheese, nuts and seeds.

Enteral feeds are normally based on the Classical KD, with ketogenic ratios for adults (perhaps 2:1 to 3:1) generally lower than those used in children, due to larger protein requirements. As there are no commercially available adult KD formulae, feeds tend to be based around the paediatric product Ketocal (Nutricia), available in liquid or powdered form and designed for children aged one to 10 years. It always requires adjustment with additional protein, carbohydrate, vitamins and minerals when used for adults. See Figure 2 for treatment criteria and treatment stages.

CURRENT BARRIERS TO ADULT TREATMENT

Adults seeking advice from their neurology teams are readily told that ketogenic therapy is too complex, unpleasant, unhealthy and only effective in children. This is due to a lack of knowledge and experience in the practicalities of modern day ketogenic therapy within the adult neurology and dietetic sector and the lack of RCT evidence to enable NHS service developments for adults.

The high fat intake required by KDs raises concerns in uninitiated healthcare professionals and patients alike. All treatment protocols involve elements of energy prescription to deliver precise control of body weight and the full lipid profile is measured at baseline, then three to six monthly onwards as part of the biochemical monitoring. The KD prescription is adjusted as often as required to optimise outcomes and, where necessary, steps can be taken to influence lipid fractions by altering dietary fat sources. A study in adults on a MAD KD for three months or longer, reported that the increased levels of total cholesterol and LDL found in the first three months, normalised within 12 months.

No cardiovascular or cerebrovascular incidents were reported in 12 adults followed for three or more years (9). Over recent years, there has been increasing interest in the potential value of low carbohydrate regimes in the management of obesity, Type 2 diabetes and metabolic syndrome, in terms of weight loss, increased serum high density lipoprotein cholesterol, increased low density lipoprotein particle size, reduced serum triglyceride levels and improved sensitivity to insulin (10, 11). It is possible that the flatter glucose/insulin profiles and the metabolic shift from fat storage towards fat oxidation induced by the KD may convey additional metabolic benefits to some adults with refractory epilepsy.

In 30 years of clinical practice, I haven't encountered a more powerful and life transforming dietary treatment than ketogenic therapy. Frustratingly, we are still unclear about the mechanisms of action and have no way of predicting who will respond and who will not. With the current limitations on the provision of ketogenic services, this knowledge would be immensely helpful. However, the potential of ketogenic diets to bring hope and a sense of control to individuals who have neither, is a powerful driver to those patients and clinical specialists in pursuit of increased availability of this century-old therapy that modern medicine cannot yet find a way to replace.

In the UK, ketogenic therapy for adults with epilepsy is provided through Matthew's Friends Clinics (www.mfclinics.com), the adult metabolic team at the National Hospital for Neurology & Neurosurgery in London and a neuropsychiatry team at The Barberry in Birmingham, with some single case provision in other centres.

For further information on ketogenic therapy including adult protocols, please see reference 12.

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Case study:

Andy, aged 50, has seizures as a result of a brain tumour.

He has been using a modified KD for three and a half years.

"I have tried a variety of different anticonvulsant drugs with varying degrees of success and failure. Some of the drugs have me made me short tempered; some of them have made me fixate on small, insignificant issues, others have just not controlled the seizures enough and I have wound up back in hospital. And all of them give me fatigue and I find this the hardest to deal with.

"Within a few weeks of starting the ketogenic diet, the intensity and frequency of my seizures decreased and, with the guidance of my neurologist, I was able to gradually taper my Clobazam dose and withdraw it completely eight months after commencing ketogenic therapy. This has resulted in a significant improvement in my concentration and overall energy levels with no worsening of the seizures. It has given me a huge chunk of my life back."

See Andy's short film at:
http://site.matthewsfriends.org/index.php?page=andy-wild

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