THE KETOGENIC DIET: AN OVERVIEW

Ali Hutton
Registered Dietitian

Ali works as a Dietitian in Medical Affairs and Marketing at Vitaflo International.

The ketogenic diet (KD) is a high fat, low carbohydrate, adequate protein diet designed to mimic the effects of fasting or starvation.[1] The KD has gone in and out of favour as a treatment for epilepsy over the years, but a recent re-emergence of interest in the use of the diet in the management of various conditions has seen it become the focus of much research.

The KD evolved from the observation that extended fasting led to significant epileptic seizure improvement[2] and the knowledge that this effect could be replicated by altering the macronutrient profile of the diet. The high fat and low carbohydrate content of the diet and the resulting reduced glucose availability and stimulus for insulin secretion, triggers a biochemical shift toward fatty acid oxidation rather than glycolysis.[3] The resulting ketones are utilised as an alternative energy source by metabolically active tissues, such as the heart, muscle and brain.[3] The exact mechanisms by which the KD exerts its anticonvulsant effect remain unknown,[2] but proposed mechanisms include alterations in oxidative stress, changes in brain neurotransmitter levels and increased mitochondrial proliferation.[4]

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VARIATIONS OF THE KD

The KD has evolved over the years and variations of the diet now exist and differ in their proportions of fat, carbohydrate and protein. The original version of the KD, or the Classical KD, uses the optimal ketogenic ratio for seizure control: usually 4:1 (90% of total energy from fat), or 3:1 (87% of total energy from fat). In 1971, Dr Peter Huttenlocker at the University of Chicago introduced the medium chain triglyceride (MCT) KD.[5] As MCT has a higher ketogenic potential than long chain triglyceride (LCT), less of the total energy in the diet must come from fat and a more liberal intake of carbohydrate and protein is allowed. The Modified Atkins Diet was introduced in 2003 as a modification of the Atkins diet for weight loss.[6] In 2005, the Low Glycaemic Index Therapy (LGIT) was offered as another option, with a more generous carbohydrate intake, but only allowing those carbohydrates with a glycaemic index of less than 50.[7] The Modified KD is an amalgamation of these diets. It is high in fat and low in carbohydrate, but does not limit protein or total dietary energy.[2]

IN THE PAST

The first known documentation of fasting as a therapeutic measure for epilepsy was in the 5th-4th century BC in the Hippocratic Corpus.[5] It was mentioned again in the 1st century AD in the *King James Bible*, where Mark relates the story of Jesus curing a boy with epilepsy through prayer and fasting.[5] In the 1920s, starvation and the KD were used by a number of physicians to treat epilepsy, but, by the late 1930s and in the 1960s, this practice was superseded by anti-epileptic drugs (AEDs) such as phenytoin and sodium valproate respectively.[5] The KD was no longer seen as justifiable and fewer dietitians were trained in its use. This meant that the KD was not implemented properly, which led to the perception that it was not effective in seizure control.[5]

The 1990s were a turning point for the KD, with publication of the results of the first multicentre prospective study on the efficacy of the KD in epilepsy management.[8] In 2008, the first

randomised controlled trial (RCT) was published by Great Ormond Street Hospital,[9] and supported the use of the KD in children with intractable epilepsy.[10] A later study in 2009 showed the MCT KD and Classical KD to be comparable in terms of efficacy and tolerability.[11]

In 1923, Otto Warburg, a German biochemist hypothesised that the primary cause of cancer was a dysfunctional metabolic process and not a genetic one.[12,13] The Warburg Effect is the observation that where normal cells use mitochondrial oxidative phosphorylation to generate the energy needed for cellular processes, cancer cells have a disturbed metabolic process and use aerobic glycolysis, which is related to their uncontrolled growth.[13] The theory was initially dismissed, but recent times have seen it become the basis of research into using the KD in the manipulation of the metabolic processes which are involved in the progression of malignant tumours.[4,12,14,15]

THE PRESENT

In 2012, the NICE clinical guidance on the diagnosis and management of epilepsy advised that children with intractable epilepsy should be referred to a tertiary paediatric specialist for consideration of a KD.[16] Despite this, there continues to be a dearth of NHS ketogenic services with suitably trained HCPs who can implement and support the KD. The KD charity Matthew's Friends (www.matthewsfriends.org) is working to raise awareness of the KD and provide HCPs with training in the administration and support of the diet.[9] NICE does not currently recommend the KD for adults with epilepsy, due to a lack of RCT data for this patient group, but a number of trials in adults are ongoing.[2]

The KD is also a recognised management option for seizures associated with neurometabolic diseases. It is recommended for the long-term treatment of seizures associated with glucose transporter type 1 deficiency syndrome (GLUT1DS) and pyruvate dehydrogenase deficiency (PDHD). The KD is efficacious in the treatment of these conditions because the metabolic blocks associated with them can be bypassed by the provision of ketones as an alternative fuel to glucose.[3]

Specialist products are available for use in the KD and include fat emulsions, oils and powder preparations. These products are intended for

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medical use only and are classed as 'foods for special medical purposes' or FSMP. Some of these products contain a high proportion of MCT and can be used in any version of the diet to improve palatability and increase flexibility, as explained above.

LOOKING TO THE FUTURE

Research into the possible future applications of the KD includes the management of neurological and neurodegenerative conditions, such as amyotrophic lateral sclerosis (ASL), traumatic brain injury, stroke, depression, Parkinson's disease and Alzheimer's disease.[17] A randomised double-blind study of patients with mild-moderate Alzheimer's disease showed that a subgroup treated with an MCT ketogenic compound showed significant improvement in cognitive function compared to controls.[18]

There is growing evidence that the KD can be used in the treatment of seizures associated with certain mitochondrial disorders.[17] For example, if seizures are caused by respiratory chain complex (e.g. electron transport chain) defects, then the KD can be utilised because fatty acid oxidation in the mitochondria bypasses the glucose oxidation pathway.[19]

In recent years, evidence has emerged that a low carbohydrate, as opposed to a low fat, diet can achieve weight loss, increase serum high density lipoprotein, increase low density lipoprotein particle size, reduce serum triglyceride levels and improve insulin sensitivity.[3,20] This raises the possibility of using the KD in the management of obesity, Type 2 diabetes and metabolic syndrome.[3,20]

An exciting area of current research is into the use of the KD as an adjuvant treatment for malignant tumours, with particular interest in the management of glioblastoma multiforme (GBM), the most malignant of primary brain cancers. Much of this research is based on Otto Warburg's observations,[12,21] as explained above.

Professor Thomas Seyfried from Boston College in the US is one of the key researchers in this area. He advocates using the KD in the management of GBM either with or without two to three days of fasting (i.e. a Restricted KD) pre-KD to promote ketosis and with or without anti-glycolytic drugs to lower glutamine levels and thus restrict fuel for tumour growth.[12] There is a general lack of RCTs on the use of the KD in the management of cancer and data to date mostly comes from animal studies and case studies.[4] There are, however, numerous clinical trials underway.[4]

The recent re-emergence of interest in the KD has opened the door to the possibility of using the diet in the management of a number of conditions. Results of ongoing studies and clinical trials are eagerly-awaited, and may hold the key to future treatment development and exciting research opportunities.