The Ketogenic Diet

The ketogenic diet is a high fat low carbohydrate diet that has been used for almost one hundred years in the treatment of epilepsy. Starvation was originally determined to be beneficial for epileptic seizures. Since this was not a practical solution, the ketogenic diet was devised to mimic the effects of starvation by taking the main energy source as fat. The use of the diet was therefore first reported for the treatment of seizures in 1921.

Over the years the Classical ketogenic diet based on the ratio of fat to carbohydrate (including protein) was used (usually 3 or 4:1). This however became less in favour with the advent of anticonvulsant medication. It was also heralded to be 'unpalatable' and causing many side effects. With the realisation however that not all children responded to anticonvulsant medication, interest was maintained in certain centres. In the early 1970s, Huttenlocher reported on a further type of ketogenic diet, still high in fat and low in carbohydrate but using medium chain triglyceride (MCT) oil to supplement each meal and boost ketosis. MCT is absorbed more efficiently than long chain fat and is carried directly in the liver. The 'MCT' diet was therefore born. The diet has continued to be used in childhood epilepsy for drug resistant cases, with increased recognition that it is the treatment of choice for certain metabolic disorders. A high level of monitoring is required; not least calculation of the diet requirements specific to each individual child along with appropriate mineral and vitamin supplementation. However, dietician resources have remained scarce. To date the rationale for lack of support has been the paucity of data supporting true efficacy, despite many open label studies more than suggesting benefit.

Does it work?

Much of the data accumulated on the efficacy of the ketogenic diet in epilepsy has been from open label cohort studies. A systematic review reported in 2000 was concerned about the possible availability and inclusion of only 11 studies, all of which were observational, only 2 of which were prospective and 9 of which were from a single centre with no evidence from randomised controlled trials. This was further highlighted by the Cochrane review, that concluded that there was no reliable evidence from randomised controlled trials to support the use of the ketogenic diet. This aside, open label studies have consistently reported that 20-40% children have a >50% improvement and a further 20-60% a >50% improvement. A more recent systematic review that only included trials with up to 6 months follow-up again commented on the lack of data from a randomised controlled trial. However, from a total of 26 studies they were able to include 14, with a collective study population of 972 patients. At 6 months 15.6% were seizure free and 33% had a >50% reduction in seizures. A further meta-analysis found 19/392 abstracts to fulfil inclusion criteria, with a collective population of 1084. They calculated a pooled odds ratio using a random effect model of treatment success amongst patients staying on the diet relative to discontinuation of 2.25 (1.69-2.98).

Recently the first randomised controlled trial comparing the ketogenic diet against no change in treatment has been published. This study reported on the three month seizure outcome in children with drug resistant epilepsy randomised to either receive a ketogenic diet after 4 weeks baseline or after a further 3 months during which there was no change in treatment. This showed responder rates on an intention to treat basis of 38% when compared to 6% in the no change group. Further 7% on the diet had a >50% reduction compared to none in the control group. These showed rates of response comparable to any new anticonvulsant medication, in a relatively drug resistant group, providing long awaited definitive evidence for its benefit. As part of the trial protocol, the ketogenic diet group were further randomised to receive either the MCT diet or the classical diet; results showed there was no significant difference in the responder rates or mean reduction in seizure frequency between the two groups. This would suggest that not only is the ketogenic diet an appropriate treatment to discuss after failure of two anticonvulsant medications but also that a degree of dietician and parent choice can be undertaken as to which diet may be used.

How does it work?

Over the years many attempts have been made from clinical summation and animal studies...
about the possible mechanism of action of the ketogenic diet. It may be that a single action is not responsible for its effect. Several biochemical changes that result from the diet have been advocated as possibly involved in the anticonvulsant action including ketone bodies, free fatty acids (especially polyunsaturated fatty acids) or glucose restriction. A link between ketosis and seizure control has both been proved and disproved; although there is evidence of ketones having anticonvulsant properties, optimal seizure control generally lags days to weeks behind the development of ketonaemia which occurs within hours of diet onset. Calorie restriction alone has been demonstrated in mice to impair seizure susceptibility. Some evidence suggests this may activate ATP sensitive potassium channels that may critically be involved in the regulation of seizure activity. Other evidence has suggested this may be boosted by free fatty acid accumulation. There are also hypotheses with regard to neurotransmitters. Much animal data has been accumulated, a full review of which is available elsewhere.

**Indications**

In general, there is no reason why the ketogenic diet cannot be considered after failure of two appropriate antiepileptic medications in the treatment of childhood epilepsy. One particular question that remains however is are there particular individuals who are more likely to respond than others, and therefore should be trialed on the diet earlier rather than later? Open label studies have reported benefit in several epilepsy syndromes, particularly in myoclonic astatic epilepsy. Dravets syndrome, and tuberous sclerosis. This aside, in the randomised controlled trial reported by Neal et al the most common side effects after three months of the diet were vomiting (13/54, 24%), constipation (18/54, 33%), lack of energy (13/54, 24%), hunger (12/54, 22%) and diarrhoea (7/54, 13%). However only 10/65 children who received the diet discontinued because of side effects prior to three months; three because of parental unhappiness with the restrictions, two with behavioural food refusal, and one each with increased seizures, extreme drowsiness, constipation, vomiting and diarrhoea. Renal stones are a theoretical risk; a study from the John Hopkins group has suggested young children with a high calcium excretion are those most at risk. Furthermore, growth may be delayed; it appears growth velocity deviates more from the expected trajectory the longer an individual is on the diet, particularly in the young. This appears to be true regardless of the type of diet used.

There are few contraindications to use of the diet. There are of course certain metabolic defects that must be excluded as the individual requires glucose for energy metabolism, such as the organic acidurias, including pyruvate carboxylase deficiency. Furthermore, although behaviour disorder per se would not be considered a contraindication, behaviour difficulties specifically related to eating should be resolved as much as possible before considering this form of treatment. Gastroesophageal reflux may of course be exacerbated in view of delayed gastric emptying from the high fat content of the diet.

**When should the diet be used in epilepsy?**

The diet cannot be thought of as a natural treatment; it has side effects just as any other anticonvulsant medication as outlined above. This aside it has now been demonstrated that it can be effective in drug resistant epilepsy when compared to no change in treatment. It should therefore be considered earlier in the natural history of childhood epilepsy when initial response to antiepileptic drugs is not seen. However, the diet requires a high level of dietetic and medical monitoring. The lack of wider availability relates to shortage of dietetic support which needs to be addressed in the long term.

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**The ketogenic diet has now been shown to be as effective as any new anticonvulsant drug in drug resistant childhood epilepsy**

**Side effects and contraindications**

As with any anticonvulsant drugs there remain side effects. The diet cannot be considered a ‘natural’ treatment. This aside, although studies suggest a high rate of side effects, few children discontinue the diet because of these, as dietary adjustment can usually resolve them. In the randomised controlled trial published by Neal et al the most common side effects after three months of the diet were vomiting (13/54, 24%), constipation (18/54, 33%), lack of energy (13/54, 24%), hunger (12/54, 22%) and diarrhoea (7/54, 13%). However only 10/65 children who received the diet discontinued because of side effects prior to three months; three because of parental unhappiness with the restrictions, two with behavioural food refusal, and one each with increased seizures, extreme drowsiness, constipation, vomiting and diarrhoea. Renal stones are a theoretical risk; a study from the John Hopkins group has suggested young children with a high calcium excretion are those most at risk. Furthermore, growth may be delayed; it appears growth velocity deviates more from the expected trajectory the longer an individual is on the diet, particularly in the young. This appears to be true regardless of the type of diet used.

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**REFERENCES**