

The Ketogenic Diet



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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.¹ 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 thereafter first reported for the treatment of seizures in 1921.²

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.³ 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 dietetic resources have remained scarce. To date the rationale for lack of support has been the paucity of data supporting true efficacy, this despite many open label studies more than suggesting benefit.^{4,5}

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.⁶ This aside, open label studies have consistently reported that 20-40% children have a >90% 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



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from a randomised controlled trial.⁷ 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).⁸

Recently the first randomised controlled trial comparing the ketogenic diet against no change in treatment has been published.⁹ 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 >90% 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.¹⁰ 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 dietetic 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.^{11,12} 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.¹² 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.¹²

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,¹³ Dravets syndrome,¹⁴ and tuberous sclerosis.^{15,16} This aside, in the randomised controlled trial reported by Neal and colleagues, no difference in efficacy was seen between focal and generalised epilepsy; more specific breakdown into individual syndromes demonstrated little benefit in one over another, not surprisingly in view of the small numbers in each group.⁹

Of course there remain metabolic defects, of which seizures may be part of the clinical phenotype, where the ketogenic diet is imperative in treatment as the ketones provide the energy source. An example would be glucose transporter defects, where glucose uptake is poor into the central nervous system and ketones provide an alternative fuel. The diet would appear important for a child to adhere to during periods of brain development but the need beyond this remains unclear.¹⁷

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 al⁹ 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.¹⁸ 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.^{19,20} This appears to be true regardless of the type of diet used.¹⁹

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. ♦

REFERENCES

1. Guelpa GMA. *La lutte contre l'épilepsie par la désintoxication et par la réduction alimentaire*. Revue de Therapie Medico-Chirurgicale 1911;78:8-13.
2. Wilder RM. *The effects of ketonemia on the course of epilepsy*. Mayo Clin Proc 1921;2:307-8.
3. Huttenlocher PR, Wilbourn AJ, Signore JM. *Medium-chain triglycerides as a therapy for intractable childhood epilepsy*. Neurology 1971;21:1097-1103.
4. Freeman JM, Vining EPG, Pillas DJ. *The efficacy of the ketogenic diet - 1998: a prospective evaluation of intervention in 150 children*. Pediatrics 1998;102:1358-63.
5. Kang HC, Kim YJ, Kim HD. *Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multi-centre experience*. Epilepsia 2005;46:272-79.
6. Levy R, Cooper P. *Ketogenic diet for epilepsy* (Cochrane review). The Cochrane Library [3]. 2004. Chichester, UK, John Wiley & Sons.
7. Keene DL. *A systematic review of the use of the ketogenic diet in childhood epilepsy*. Pediatr Neurol 2006;35:1-5.
8. Henderson CB, Filloux FM, Alder SC, Lyon JL, Caplin DA. *Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis*. J Child Neurol 2006;21:193-8.
9. Neal EG, Chaffe HM, Schwartz RH et al. *The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial*. Lancet Neurol 2008;7:500-6.
10. Neal EG, Chaffe HM, Schwartz RH et al. *A randomised controlled trial of classical and medium chain triglyceride ketogenic diets in the treatment of childhood epilepsy*. Epilepsia 2008;49:1-9.
11. Hartman A, Gasior M, Vining EP, Rogawski MA. *The neuropharmacology of the ketogenic diet*. Pediatr Neurol 2007;36:281-92.
12. Bough KJ, Rho JM. *Anticonvulsant mechanisms of the ketogenic diet*. Epilepsia 2007;48:43-58.
13. Oguni H, Tanaka T, Hayashi K, et al. *Treatment and long term prognosis of myoclonic astatic epilepsy of early childhood*. Neuropediatrics 2002;33:122-32.
14. Caraballo RH, Cersosimo RO, Sakr D, Cresta A, Escobal N, Fejerman N. *Ketogenic diet in patients with Dravet syndrome*. Epilepsia 2005;46:1539-44.
15. Kossoff EH, Thiele EA, Pfeifer HH, McGrogan JR, Freeman JM. *Tuberous sclerosis complex and the ketogenic diet*. Epilepsia 2005;46:1684-6.
16. Coppola G, Klepper J, Ammedola E et al. *The effects of the ketogenic diet in refractory partial seizures with reference to tuberous sclerosis*. Eur J Paediatr Neurol 2006;10:148-51.
17. Klepper J, Leidencker B. *GLUT1 deficiency syndrome-2007 update*. Dev Med Child Neurol 2007;49:707-16.
18. Furth SL, Casey JC, Pyzik PL et al. *Risk factors for urolithiasis in children on the ketogenic diet*. Pediatr Nephrol 2000;15:125-8.
19. Neal EG, Chaffe HM, Edwards N, Lawson M, Schwartz R, Cross JH. *Growth of children on classical and medium chain triglyceride ketogenic diets*. Pediatrics 2008;In press.
20. Vining EP, Pyzik PL, McGrogan JR et al. *Growth of children on the ketogenic diet*. Dev Med Child Neurol 2002;44:796-802.