The Ketogenic Diet in the Treatment of Childhood Epilepsy

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Abstract

The ketogenic diet has been used for the treatment of drug-resistant epilepsy in childhood for almost 100 years. This aside, it is only over the past decade that renewed interest has led to a further evidence base for efficacy, evaluation of optimal implementation and wider discussion of possible mechanisms of action. Randomised controlled data have now demonstrated the diet to be as effective as any newer anti-epileptic drug (AED) in drug-resistant epilepsy. Implementation can be challenging, and is resource-intensive, but successful use can lead to improved quality of life with most immediate side effects alleviated by dietary manipulation. However, data are still required on the choice of optimal candidates and the role of alternative diets in older children.

Keywords

Ketogenic diet, epilepsy, childhood, drug-resistant

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The ketogenic diet (KD) is a high-fat diet used in the management of childhood epilepsy. It was determined in the early part of last century that starvation could have a beneficial effect on seizure control.[1–3] Realising that this was not practical, Wilder in 1921 suggested that designing a diet that may mimic the effects of starvation – namely with fat as the main source of energy that is metabolised to ketones – could consequently have a similar effect on epileptic seizures.[4] Subsequently, a colleague confirmed the beneficial effect of the then so-called 'classic ketogenic diet'.[5] Following this, its use became widespread, but with the advent of anticonvulsant medication, in particular phenytoin in the 1930s, its use became less favoured. However, in time it became evident that medication was not the solution for all and there was a resurgence in the popularity of the KD.

The original diet was composed of predominantly long-chain fats and was based on the ratio of fat to carbohydrate and protein (3:1 or 4:1), the so-called classic KD. Over the years it became evident that there was some concern about tolerability. In 1971 Huttenlocher reported on the use of an alternative fat – medium-chain triglyceride (MCT), which is more ketogenic per calorie than long-chain fat – as a supplement, and the MCT diet was born.[6] However, of note this diet still remained low in carbohydrate. Subsequent use of the KD has been variable, with consideration in management dependent on the experience of individual professionals. However, the evidence base is now increasing as regards benefits of the diet in drug-resistant epilepsies of childhood and, more specifically, particular epilepsy syndromes.

The Evidence Base for Efficacy – Does It Work?

Many open-label retrospective and prospective studies have reported on the use of the diet in the treatment of childhood epilepsy. However, the quality of such studies has been variable. In 2000 a systematic review reported on studies evaluating the KD and its use in childhood epilepsy.[7] Of note was the fact that only 11 studies fulfilled the criteria for the review. All 11 were observational, only two had been carried out on a prospective basis and nine out of the 11 were from a single institution. Since then there has been a steady increase in the number of publications from both a clinical and a basic science perspective. A further systematic review in 2006 of articles since 1990 found only 26 studies, 14 of which met the criteria for inclusion, which included up to six-month outcome data on the diet.[8] There were 17 Class Two studies that could be included. This gave a total collective population of 972 children. At six months, 15.6% were seizure-free and 33% had more than a 50% reduction of seizures. However, it was also emphasised that there were no randomised controlled data and the author stated that these were desperately needed in order to verify the effect of the diet in line with assessment of anti-epileptic medications.

More recently, the first randomised controlled trial was published of use of the KD in drug-resistant epilepsy in childhood.[9] This

randomised 145 children between two and 16 years of age who had at least daily seizures and failed to respond to at least two anti-epileptic drugs (AEDs). Children were randomly assigned to receive a KD either after a four-week baseline period of seizure documentation or after a further three-month delay when there was no change in treatment; the latter was the 'control' group. The primary end-point of this study was reduction in seizures; tolerability of the diet was also assessed. Of the 145 children, 73 were assigned to the KD and 72 to the control group. At three months, data from 103 children were available for analysis (54 on the KD and 49 controls). The percentage of baseline seizures was significantly lower in the diet group than among the controls (62 versus 136%) and, with regard to responder rates (>50% reduction in seizures), 28 children in the KD group achieved this compared with four (6%) controls. This result reached significance. Further analysis was performed as the KD group was randomised to either the classic KD or the MCT diet. At no time-point – namely three, six or 12 months – was there a significant difference in efficacy, either in percentage of baseline seizures or in responder rates.[10]

One further randomised controlled study has been published: a double-blind study assessing children with Lennox-Gastaut syndrome.[11] Children were initially fasted and subsequently clinical and electroencephalogram (EEG) events were documented. Children were randomised to receive a KD with either a glucose drink or a saccharin drink. Children and parents were unaware which of the diets they were on. After six days they then crossed over to receive the alternative drink. Seizure count and EEG data were recorded at this point and again after a further six days. No significant difference in electrical or clinical events were noted between the KD and the non-KD (glucose drink) period. However, the methodology may have precluded ultimate significance in view of the fact that the baseline seizure frequency was documented after a 36-hour period of fasting and subsequently children receiving the glucose drink did not come out of ketosis.

How Well Tolerated Is the Ketogenic Diet – Is It Palatable?

There has been a wide belief that side effects are problematic on the KD. These can be divided into two categories: those that can be seen in the short term, most of which can be alleviated with alterations to the diet; and those that may be seen to be a concern over a prolonged duration of the use of the diet. The diet cannot be seen to be a natural treatment, although parents often interpret it as such.

In the short term, in the randomised controlled trial reported[9,10] as well as in data from open-label studies,[8,12,13] vomiting, diarrhoea, constipation and hunger are the most commonly reported side effects; however, there were very few withdrawals at three months in the randomised controlled trial due to these side effects, which on the whole resolved with manipulation of the diet. Furthermore, no significant difference was seen between the classic and the MCT diet with regard to these side effects at either three or 12 months.[10] Constipation is a common problem seen with both diets, seen in up to 45% of the population at any one time. Manipulation of the diet as well as use of non-absorbable laxatives is a common way forward. Hunger should be alleviated as with the appropriate calorie intake this should not be an issue. Parents are often concerned about the volume of food as smaller portions are seen on a high-fat diet, and such concern needs to be alleviated.

High serum cholesterol is of concern; this is seen with both the classic and the MCT diet. The long-term implications of this in terms of heart disease are unclear, due to the poor performance of prognostic indicators in childhood for future development of heart problems. This aside, triglycerides, although they may increase on the classic diet, do not increase on the MCT diet, and in the presence of family history the latter diet may be more appropriate. In the long term, a risk of renal calculi has been reported. On further evaluation, children who may be at particular risk are those who are young, have a poor fluid intake and are non-ambulant. Furthermore, children with a high calcium excretion are also at risk.[14] Although children need to be monitored for the occurrence of such, if they do occur they rarely require dietary discontinuation and may be alleviated with administration of citrates. The latter may be routinely given alongside the diet in some centres.

In the longer term children appear to bruise more easily while on the KD, and this has to be carefully monitored in view of the inaccurate conclusions that may be drawn from the occurrence of unexplained bruising. Children studied in detail with regard to this symptom have been found to have prolonged bleeding times with abnormalities in platelet aggregation,[15] but these do not preclude safety during surgical procedures.[16] Of greater concern has been the growth of children on the KD. Growth appears to be restricted with a negative change in z-score – that is, a deviation of height velocity away from the expected with increasing duration on the diet; this is particularly noticeable in the very young.[17] Although originally it was thought that this might be due to the low protein in the diet (although this is kept to recommended daily intake), a further study has demonstrated this not to be the case with similar changes seen on an MCT and classic diet.[18]

With administration of the diet supplementation is required to ensure appropriate mineral and vitamin intake. Mineral and vitamin deficiencies have been reported, with clinical consequences.[19,20] Despite appropriate supplementation using standardised vitamin preparations, changes in vitamin A and vitamin E were seen in children in the randomised controlled trial over time, of uncertain significance.[21] No change in plasma zinc was seen, but plasma selenium decreased slightly in the group as a whole. However, more notably there was a marked decrease in mean plasma magnesium within the classic diet group. There has also been increasing concern about vitamin D deficiency.[22] Further data suggest that these children are at risk prior to initiating the diet and therefore this needs to be carefully monitored. In the longer term a possible increased risk of fractures has been suggested, although this needs verification.[23] Monitoring therefore needs to be undertaken on at least a six-monthly basis of mineral and vitamin values to determine whether additional supplementation is required.

Specific Indications or Contraindications to the Use of the Diet

The premise of the KD is that an individual will be able to switch from carbohydrate to fat as the primary fuel for energy. Absolute contraindications therefore include metabolic defects that lead to decompensation should glucose/carbohydrate not be readily available. This would include such defects as pyruvate carboxylase deficiency and fatty acid oxidation defects.[24] There are of course also specific defects where ketones provide a 'bypass' to a fuel that is not otherwise available, such as glucose transporter defects (GLUT1

deficiency) and pyruvate dehydrogenase deficiency. Furthermore, the phenotype of the epilepsy associated with GLUT1 deficiency may be wider than previously thought, with implications for the applicability of the KD in a wider population.[25] Previous suggestions that mitochondrial defects may be a contraindication to use of the KD now appear to be unfounded, with reports of successful use[26] and even data to suggest the diet may be of benefit.[27]

Behavioural problems overall are not a contraindication to the use of the diet, with such problems being common co-morbidities among children with complex epilepsy. This aside, behavioural issues around feeding times are a problem and need to be addressed prior to introduction. Furthermore, gastro-oesophageal reflux may be exacerbated by a high-fat diet due to delayed gastric emptying with high fat content.

Although data from the randomised controlled trials have not indicated specific efficacy in individual epilepsy syndromes,[9] the relatively small numbers involved probably preclude this. Certainly, data from other open-label trials suggest some epilepsy syndromes where the KD may be considered sooner rather than later, e.g. myoclonic astatic epilepsy[28] and severe myoclonic epilepsy of infancy.[29] There are also data to suggest efficacy in infantile spasms,[30] although differing availability of individual medications across countries may predetermine treatment protocols. There has also been a further suggestion about the role of the diet in the acute management of cluster seizures[31] or status epilepticus.[32]

Role of Medication

The KD needs to be considered as additional anti-epileptic medication in the management of children with epilepsy. Consequently, introduction and weaning of other drugs is managed as in any other such situation. There is little information on the pharmacodynamic interactions that may occur with AEDs; this aside, there is also no evidence that serum levels will be affected by such a diet.[33] The possible increased risk of some side effects may need to be monitored if the child is also taking other medications with a similar risk profile to the KD; an example is renal calculi if the child is taking topiramate or zonisamide, although to date there is no evidence that this is problematic.[34] Since the KD may be considered alongside other AEDs, there is also no reason why the latter cannot be weaned completely and children left on the KD alone if effective.

Alternative Diets?

The KD in the classic or the MCT form has been noted to be very restrictive. Certainly, in the older population, namely teenagers and even adults, its use has been very limited in view of the concerns about hunger and poor tolerability. Use in adults has been reported but to a very limited degree, with limited recruitment into trials and high drop-out rates, primarily due to poor tolerability and lack of effect.[35] This aside, there may also be an issue about satiety versus hunger and the fact that adults have very different views about food intake from children, who will cease eating once full. In view of the restriction of the diet, other diets with similar effects on the body have been suggested – in the first instance the modified Atkins diet. This is very similar to the KD: a high-fat, low-carbohydrate diet but with a major difference of unlimited protein. A suggested limit of 20g of carbohydrate per day is given with no caloric or protein restriction.[36] In a limited open-label study of 30 adults 18–50 years of age, 10 discontinued the diet before three months, but on an intention-to-treat analysis 47% had more than a 50% reduction of seizures in three months. In a larger study in children a similar efficacy was demonstrated with similar retention rates. A further alternative suggested is the low-glycaemic-index diet, where the complexity of sugars is noted within the intake. The glycaemic index is calculated from the incremental area under the blood glucose curve after feeding; therefore, more complex sugars not leading to to a rapid rise in blood sugar have a low glycaemic index.[37] In a series of children reported from the Massachusetts General Hospital in Boston, 76 children were trialled, 50% of whom had more than a 50% reduction of seizures at three months, although 49 of the children discontinued the diet after a period of two to 108 weeks. These alternative diets require further evaluation as to their role, particularly in the older population (teenagers and adults) and in those where true dietary restriction is difficult.

Mechanisms of Action – Towards a Pill?

Basic science research has attempted to elucidate the possible anti-epileptogenic (and potentially neuroprotective) effects of the KD.[27,38] Many systemic and metabolic changes are induced, but, as with many of the anti-epileptic medications, it is unclear which changes are the most relevant. Early studies suggested that seizure reduction was related to the degree of ketosis; however, the relationship is not direct and, although acetone has been shown to prevent acutely provoked seizures in animals, there is no evidence that ketone bodies can have a direct effect on synaptic transmission or neuronal excitability. Experimental data have also suggested an increase in mitochondrial biogenesis and energy metabolism, or a role for polyunsaturated fatty acids.[27] It is likely that the underlying changes induced by the KD are multiple and synergistic in their anti-epileptic effect,[39] and it therefore appears unlikely that in the immediate future the diet will be replaced by a simple medication or pill alone.

Ways Forward

There is little question that evidence is now weighted in favour of the efficacy of the KD in the treatment of childhood epilepsy. The question remains as to when it should be offered in the natural history of childhood epilepsy. Few would question the current practice of considering the diet should two AEDs fail. However, currently the resource is not sufficiently available (in view of dietician time) for this to be offered widely. Following the acknowledgement that data are now more readily available but insufficient to compose true guidelines, an international consensus document has been published to guide on the optimal implementation of the KD, acknowledging areas that require further work.[24] There is no question that further data are required, not least to evaluate the role of the diet in the younger population and specific epilepsy syndromes, the role of alternative diets and the role of the KD in conditions other than epilepsy. ■

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1. Guelpa GMA, La lutte contre l'epilepsie par la desintoxication et par la reducation alimentaire, *Revue de Therapie Medico-Chirurgicale*, 1911;78:8–13.
2. Geyelin HR, Fasting as a method for treating epilepsy, *Medical Record*, 1921;99:1037–9.
3. Conklin HW, Cause and treatment of epilepsy, *Am J Osteopth Ass*, 1922;26:11–14.
4. Wilder RM, The effects of ketonemia on the course of epilepsy, *Mayo Clin Proc*, 1921;2:307–8.
5. Peterman MG, The ketogenic diet in epilepsy, *JAMA*, 1925;84:1979–83.
6. Huttenlocher PR, Wilbourn AJ, Signore JM, Medium-chain triglycerides as a therapy for intractable childhood epilepsy, *Neurology*, 1971;21:1097–1103.
7. Lefevre F, Aronson N, Ketogenic diet for the treatment of refractory epilepsy in children: a systematic review of efficacy, *Pediatrics*, 2000;105:e46.
8. Keene DL, A systematic review of the use of the ketogenic diet in childhood epilepsy, *Pediatr Neurol*, 2006;35:1–5.
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*, 2009;50:1109–17.
11. Freeman JM, Vining EP, Kossoff EH, et al., A blinded, crossover study of the efficacy of the ketogenic diet, *Epilepsia*, 2009;50:322–5.
12. 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.
13. Kang HC, Kim YJ, Kim HD, Efficacy and safety of the ketogenic diet for intractable childhood epilepsy: Korean multi-centre experience, *Epilepsia*, 2005;46:272–9.
14. Furth SL, Casey JC, Pyzik PL, et al., Risk factors for urolithiasis in children on the ketogenic diet, *Pediatr Nephrol*, 2000;15:125–8.
15. Berry-Kravis E, Booth G, Taylor A, Berman W, Bruising and the ketogenic diet: evidence for diet induced changes in platelet function, *Ann Neurol*, 2001;49:98–103.
16. Hanna BG, Miller F, Ketogenic diet and surgery, *Dev Med Child Neurol*, 2001;43:847–8.
17. Vining EP, Pyzik PL, McGrogan JR, et al., Growth of children on the ketogenic diet, *Dev Med Child Neurol*, 2002;44:796–802.
18. Neal EG, Chaffe HM, Edwards N, et al., Growth of children on classical and medium chain triglyceride ketogenic diets, *Pediatrics*, 2008;122:e334–40.
19. Bergqvist AG, Chee CM, Lutchka L, et al., Selenium deficiency with cardiomyopathy: a complication of the ketogenic diet, *Epilepsia*, 2003;44:618–20.
20. Willmott NS, Bryan RA, Case report: scurvy in an epileptic child on a ketogenic diet with oral complications, *Eur Arch Ped Dent*, 2008;9:148–52.
21. Christodoulides SS, Neal EG, Fitzsimmons G, et al., Vitamin A and E, zinc, selenium and magnesium levels over 12 months on the classical and MCT ketogenic diet, *Epilepsia*, 2010, submitted.
22. Bergqvist AG, Schall JI, Stallings VA, Vitamin D status in children with intractable epilepsy and impact of the ketogenic diet, *Epilepsia*, 2007;48:66–71.
23. Groesbeck DK, Bluml RM, Kossoff EH, Long-term use of the ketogenic diet in the treatment of epilepsy, *Dev Med Child Neurol*, 2006;48:978–81.
24. Kossoff EH, Zupec-Kania BA, Amark P, et al., Optimal clinical management of children receiving the ketogenic diet: recommendations of the international ketogenic diet study group, *Epilepsia*, 2008;47:1–14.
25. Suls A, Mullen SA, Weber YG, et al., Early-onset absence epilepsy caused by mutations in the glucose transporter GLUT 1, *Ann Neurol*, 2009;66:415–19.
26. Kang HC, Lee YM, Kim HD, et al., Safe and effective use of the ketogenic diet in children with epilepsy and mitochondrial respiratory chain complex defects, *Epilepsia*, 2007;48:82–8.
27. Bough KJ, Rho JM, Anticonvulsant mechanisms of the ketogenic diet, *Epilepsia*, 2007;48:43–58.
28. 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.
29. Caraballo RH, Cersosimo RO, Sakr D, et al., Ketogenic diet in patients with Dravet syndrome, *Epilepsia*, 2005;46: 1539–44.
30. Kossoff EH, Hedderick EF, Turner Z, Freeman JM, A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms, *Epilepsia*, 2008;49:1504–9.
31. Villeneuve N, Pinton F, Bahi-Buisson N, et al., The ketogenic diet improves recently worsened focal epilepsy, *Dev Med Child Neurol*, 2009;51:276–81.
32. Abend NS, Dlugos DJ, Treatment of refractory status epilepticus:literature review and a proposed protocol, *Pediatr Neurol*, 2008;38:377–90.
33. Dahlin MG, Beck OC, Amark PE, Plasma levels of antiepileptic drugs in children on the ketogenic diet, *Pediatr Neurol*, 2006;35:6–10.
34. Kossoff EH, Pyzik PL, Furth SL, et al., Kidney stones, carbonic anhydrase inhibitors and the ketogenic diet, *Epilepsia*, 2002;43:1168–71.
35. Mosek A, Natour H, Neufeld MY, et al., Ketogenic diet treatment in adults with refractory epilepsy: a prospective pilot study, *Seizure*, 2009;18:30–33.
36. Kossoff EH, McGrogan JR, Bluml RM, et al., Modified Atkins diet is effective for the treatment of intractable pediatric epilepsy, *Epilepsia*, 2006;47:421–4.
37. Pfeifer HH, Thiele EA, Low-glycaemic index treatment: a liberalized ketogenic diet for treatment of intractable epilepsy, *Neurology*, 2005;65:1810–12.
38. Hartman AL, Gasior M, Vining EPG, Rogawski MA, The neuropharmacology of the ketogenic diet, *Pediatr Neurol*, 2007;36:281–92.
39. Rho JM, Sankar R, The ketogenic diet in a pill: is this possible? *Epilepsia*, 2008;49(s8);127–33.