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The ketogenic diet—update on recent clinical trials

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SUMMARY

The ketogenic diet (KD) has been used in the treatment of epilepsy for almost 100 years. Several cohort studies have emphasized its possible benefit, although use became less at the introduction of anticonvulsant medication. However, the KD has regained recognition over the past 15 years. Resources remain scarce and its availability for children may be limited. One argument has been the lack of evidence from suitably designed trials. Systematic reviews and meta-analyses have revealed that studies are limited to class 3 and 4 data. A recently published randomized controlled trial has shown that the benefit of the KD is equivalent to any of the new anticonvulsant medications, emphasizing the need for more resources to ensure greater diet availability.

KEY WORDS: Clinical trials, Ketogenic diet, Epilepsy, Childhood.

Fasting was first found to be effective in the treatment of seizures early in the past century and several authors reported benefit (Guelpa & Marie, 1911; Geyelin, 1921). In Geyelin's study, 20/26 fasted patients had improved seizure control, two of whom remained seizure free for more than a year, with an arbitrary length of fasting of 20 days. Geyelin was inspired by the work of Conklin (1922), an osteopath, who believed that epilepsy was caused by intoxication from Peyer's patches of the intestine; therefore, he advocated complete gut rest. Conklin fasted his patients for up to 25 days, and reported a 90% success rate in children under the age of 10 years, decreasing to 50% in adults.

Use of fasting to treat epilepsy had obvious clinical limitations. It was therefore suggested by Wilder (1921) that a diet high in fat and low in carbohydrate might mimic the ketotic effect. A restriction of dietary carbohydrate would limit glucose supply, and as fat is metabolized to ketone bodies, these would be used as the alternative fuel. Wilder found that half of his patients at the Mayo Clinic had significant seizure control on this ketogenic diet (KD). Peterman (1925), also at Mayo, reported further success in a group of 37 patients, with 95% showing improvement when treated by the diet.

In 1927, Talbot et al. showed that this KD caused similar biochemical changes as fasting. They introduced the idea of an initial fast before commencing the diet, with a gradual build up of dietary fat over the following few days. The diet was subsequently shown to have a use in seizure control by many others (Helmholtz, 1927; Lennox, 1928; Wilkins, 1937). It was widely used throughout the 1930s, and was found to be most successful in children, who produce and use ketones more rapidly and have fewer problems with compliance. However, although increased numbers of studies have been published, more stringent appraisal of data quality have led to a continued lack of appreciation and use of the KD.

DATA AVAILABLE

Several cohort series have reported efficacy, of both the classical KD and variations including the medium chain triglyceride (MCT) diet (Table 1). A systematic review identified 11 studies published since 1970 that met inclusion criteria for detailed analysis (Lefevre & Aronson, 2000). No controlled study has directly compared the diet to drug therapy or surgery; in general, all patients had failed or were intolerant of treatments with multiple drug regimens. Nine of the 10 published articles were retrospective clinical series of patients treated at a single institution. Of the two further studies, one was a prospective multicenter uncontrolled trial enrolling 51 patients from seven clinical centers. The final series was a prospective study of consecutive patients treated at the same institution. Combined analysis of the outcome data showed a combined point estimate of percentage of patients who became seizure free to

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Table 1. Summary of literature on efficacy of ketogenic diet

Study & location	No.	Age (years)	Diet type	Seizure free	>90% decrease	>50% decrease
Berman, 1978 (U.S.A.)	18	2–17	MCT	1/18 (6%)	Not stated	6/18 (33%)
Coppola et al., 2002 (Italy)	56	1–23	Classical 4:1	Not stated	Not stated	37.5% at 3 months 26.8% at 6 months 17.9% at 12 months
DiMario & Holland, 2002 (U.S.A.)	24	1–15	Not stated	4/24 (17%) at 6 months 4/24 (17% at 12 months	Not stated Not stated	13/24 (54%) at 6 months 7/24 (29%) at 12 months
Freeman et al., 1998 (U.S.A.)	150	1–16	Classical 3:1–4:1	4/150 (3%) at 3 months 5/150 (5%) at 6 months 11/150 (7%) at 12 months	50/150 (33%) at 3 months 48/150 (32%) at 6 months 41/150 (27%) at 12 months	89/150 (60%) at 3 months 77/150 (51%) at 6 months 75/150 (50%) at 12 months
Hassan et al., 1999 (Canada)	52	Not stated mean 5.5	Classical 4:1(49) Modified MCT (3)	6/52 (11.5%)	Not stated	35/52 (67.3%)
Hopkins & Lynch, 1970 (Australia)	34	1–13	Classical 3:1	3/34 (8.8%)	Not stated	Not stated
Huttenlocher et al., 1971 (U.S.A.)	12	2.5–16	MCT	4/12 (33%)	Not stated	Not stated
Huttenlocher, 1976 (U.S.A.)	18	1.5–18	MCT	4/18 (22%)	10/18 (56%)	16/18 (89%)
Janaki, 1976 (India)	15	0–30	Classical 4:1	3/15 (20%)	Not stated	15/15 (100%)
Kankirawatana et al., 2001 (Thailand)	35	0.2–13	Classical 4:1	5/35 (14%) at 3 months 4/35 (11%) at 6 months 3/35 (9%) at 12 months	15/35 (43%) at 3 months 12/35 (34%) at 6 months 8/35 (23%) at 12 months	17/35 (49%) at 3 months 15/35 (43%) at 6 months 10/35 (29%) at 12 months
Kang et al., 2005 (Korea)	199	0.5–17.5	Classical 4:1	70/199 (35%) at 3 months 66/199 (33%) at 6 months 50/199 (25%) at 12 months	Not stated	123/199 (62%) at 3 months 115/199 (58%) at 6 months 82/199 (41%) at 12 months
Katyal et al., 2000 (U.S.A.)	48	Not stated	Classical 3:1 – 5:1	Not stated	16/48 (33%)	30/48 (63%) at 45 days
Kinsman et al., 1992 (U.S.A.)	58	1–19.6	Classical 4:1	Not stated	17/58 (29%)	22/58 (38%)
Mackay et al., 2005 (Australia)	26	2.3–13.2	Classical, 3:1–4.2:1	4/26 (15%)	5/26 (19%)	7/26 at 3 months (27%) 4/26 at 6 months (15%) 8/26 at 12 months (31%)
Mak et al., 1999 (Taiwan)	13	3–13	MCT	None	5/13 (38%)	7/13 (54%)
Maydell et al, 2001 (U.S.A.)	143	0.3–29	Classical 4:1	21/143 (15%) at 3 months 24/143 (17%) at 6 months 23/143 (16%) at 12 months	43/143 (30%) at 3 months 41/143 (29%) at 6 months 38/143 (27%) at 12 months	59/143 (41%) at 3 months 60/143 (42%) at 6 months 54/143 (38%) at 12 months
Ross et al., 1985 (U.S.A.)	9	0.25–13	MCT	2/9 (22%) at 10 weeks	Not stated	6/9 (66%) at 10 weeks
Schwartz et al., 1989a (UK) Schwartz et al., 1989a (UK)	59	<5–>15	Classical 4:1 (15), MCT (22), modified MCT (13), Mixed (9)	Not stated	26/63 studies on 55 children (41%)	51/63 studies on 55 children (81%)
Sills et al., 1986 (UK)	50	2–15	MCT	8/50 (16%)	12/50 (24%)	22/50 (44%)
Trauner, 1985 (U.S.A.)	17	1–13	MCT	5/17 (29%)	Not stated	10/17 (59%)
Vining et al., 1998 (U.S.A. multicentre)	51	1–8	Classical 4:1	6/51 (12%) at 3 months 6/51 (12%) at 6 months) 5/51 (10%) at 12 months	13/51 (25%) at 3 months 15/51 (29%) at 6 months) 11/51 (22%) at 12 months	28/51 (54%) at 3 months 27/51 (53%) at 6 months) 20/51 (40%) at 12 months

MCT, medium chain triglyceride.

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be 15.8% (11–21.7), 32% (25.3–39.8) >90% reduction of seizures, and 55.8% (41.2–69.7) >50% reduction. Adverse events were not consistently reported. From this review, the authors concluded that approximately half of children with refractory epilepsy would have a clinically meaningful improvement after treatment and that there was sufficient evidence to state that the diet is efficacious, although they were concerned about the lack of controlled trials.

The absence of randomized controlled data was highlighted in a Cochrane review, which concluded that no reliable evidence was available to support the use of the KD for epilepsy (Levy & Cooper, 2004). An updated systematic review (Keene, 2006) came to the same conclusion. Twenty-six studies were analyzed, 14 of which fulfilled the inclusion criteria (outcome data available at 6 months after initiating diet). The total collective population was 972 patients. At 6 months, an average of 15.6% (10.4–20.8) had become seizure free, 33% (24.3–41.8) were reported to have achieved >50% reduction in seizure frequency. Another meta-analysis (Henderson et al., 2006) extracted data from 19/392 abstracts where data were available for patients who had remained on the KD and those who had ceased at specific time points with a collective population of 1,084, with a mean age about 6 years. They calculated a pooled odds ratio using a random effect model of treatment success among patients staying on the diet relative to discontinuation of 2.25 (1.69–2.98), highlighting a need for further study of the diet's effect on different seizure types, long-term outcome and reasons for discontinuation.

Assessment of Evidence Base—Why the Standard Required?

With the increasing number of treatments available for epilepsy, some attempt at standardization of assessment of such treatments is required. Lack of support for the KD, and particularly for resources for the diet, have been attributed to the lack of an evidence base, namely, randomized controlled trials. Randomization is desirable in a treatment trial, as it limits the potential for selection bias. Precision of such trials is also determined by sufficient sample size with accurate assessment of outcome endpoints. Trials to assess efficacy in pediatric epilepsy have been lacking; in the National Institute for Clinical Excellence Health Technology Appraisal of Newer Drugs for Epilepsy in Children (Connock et al., 2006), only 20 randomized controlled trials could be found, including 15 full publications and five abstracts.

The quality of evidence to assess treatments may be graded. Such grading schemes may be akin to that proposed by the American Academy of Neurology (Hirtz et al., 2003; Table 2). Recent International League Against Epilepsy (ILAE) guidelines on evidence based analysis of antiepileptic drug (AED) efficacy proposed further criteria to assess randomized controlled trials, as well as details on primary outcome variables, minimal duration of treatment, potential for bias, detectable noninferiority boundary based upon actual sample size (accepting a positive superiority trial or sample size large enough to show noninferiority with ≤20% difference between treatment arms based on 80% power), and statistical analysis (Glauser et al., 2006). Data to date on the efficacy of the KD remains class III at best, as highlighted in systematic reviews (Lefevre & Aronson, 2000; Levy & Cooper, 2004; Keene, 2006).

Recent Clinical Trials

A randomized controlled trial of KD efficacy has now been published (Neal et al., 2008a). Children age 2–16 years who had failed at least two AEDs and had at least seven seizures per week were randomized (after a four week baseline) to either the KD or control group. After 3 months, the control group began KD treatment. Children were also randomized to receive either the classical or the MCT diet. As no difference was found in efficacy between the two groups for the initial 3 months, the two diet groups were combined for analysis. Seizure records were reviewed

Table 2. Evidence classification scheme of the American Academy of Neurology: Rating of therapeutic articles[a]

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population
- (a) Primary outcome(s) is/are clearly defined
- (b) Exclusion/inclusion criteria are clearly defined
- (c) Adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias
- (d) Relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences

Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above or a randomized controlled trial in a representative population that lacks one criteria a–d.

Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment

Class IV: Evidence form uncontrolled studies, case series, case reports, or expert opinion

[a]Taken from Hirtz et al., 2003.

for efficacy and tolerability at 3 months; thereafter, if children remained on the KD, they were reviewed at 6 and 12 months. Laboratory investigations, anthropometry, and EEG were performed at baseline, 3, 6, and 12 months.

One hundred forty-five children were randomized; 73 children to immediate dietary treatment and 72 to undergo the control period. Data from 103 children were available for analysis: 54 diet, 49 control. Sixteen children did not receive their intervention, 16 did not provide adequate data and 10 children withdrew from diet treatment before 3-month review, 6 due to intolerance. After 3 months, the mean percentage of baseline seizures was significantly lower in the diet group. On intention-to-treat analysis, 28 of the diet group had greater than 50% seizure reduction (38%), compared to four controls (6%) ($p < 0.0001$) and five of the diet group had greater than 90% seizure reduction (7%), compared to no controls ($p > 0.05$). There was no significant difference in efficacy between symptomatic generalized or symptomatic focal epilepsies. Most frequently cited side effects at 3 months were constipation, vomiting, lack of energy, and hunger; there were 10 withdrawals due to parental dissatisfaction, food refusal, increased seizures, drowsiness, constipation, vomiting, or diarrhea.

This randomized controlled trial demonstrates that the KD is significantly beneficial in the treatment of drug resistant epilepsy compared to no change in treatment. This study justifies consideration of the KD alongside any other AED in the treatment of drug resistant epilepsy.

What Diet to Use?

There have been many claims that the classical KD is more efficacious than the MCT diet, mainly originating from centers in the United States. These claims are not backed by scientific evidence, as studies comparing the efficacy of the two types of diet are very limited. Livingstone et al. (1977) examined 600 patients on the classical 3:1 KD and 25 on the MCT diet, and concluded that only those on the classical diet responded. This uncontrolled study had too large a difference in the sample size of each group for statistical analysis. Berman (1978) also compared the classical 4:1 KD and MCT diet in a small, uncontrolled group of children; he concluded that the MCT diet was less effective.

Schwartz et al. (1989a, 1989b) compared the clinical and metabolic effects of three types of KD—the classical 4:1 diet, the traditional MCT oil diet (60% energy as MCT), and the modified MCT diet (30% energy as MCT). Fifty-five children and four adults were studied. Fifteen patients received the classical diet alone, 22 received the MCT diet alone (including the four adults), 13 received the modified diet alone, and nine were given the MCT diet for at least 33 months, then changed to the classical diet. They found all three diets equally effective in controlling seizures in children under the age of 15 years. However, participants were not randomized and diets were assigned based primarily on family preference; therefore, the results could be influenced by substantial selection bias.

In the randomized trial discussed above (Neal et al., 2008a), of the 145 children who were randomized, 125 received dietary treatment at some stage (61 classical and 64 MCT). After 3, 6, and 12 months, there were no significant differences in the mean percentage of baseline seizures between the two diet groups (Neal et al., 2008b). There were also no significant differences in responder rates at any time point or in tolerability or withdrawals at 3 or 6 months. At 12 months, there were significantly more children with a history of vomiting in the classical KD group, but no other reported side effect reached significance between the two groups.

What Is Next?

Although one recent randomized trial has demonstrated efficacy of the KD approaching that of any new AED (Neal et al., 2008a), further data are required. Although this study compared efficacy in generalized versus focal epilepsy, the numbers for individual syndromes were too small for statistical analysis. Although small open label studies suggest some groups of patients may attain particular benefit, further multicenter prospective studies should define which patients would benefit most from the KD, optimal timing of diet initiation, and how long individuals should remain on treatment. Data are also required in younger children, as well as a longer-term review of retention, dropouts, and adverse effects.

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Conflict of interest: We confirm that we have read the Journal's position involved in ethical publication and affirm that this report is consistent with those guidelines.

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