Original Article

Efficacy of the Ketogenic Diet as a Treatment Option for Epilepsy: Meta-analysis

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ABSTRACT

The evidence base for the efficacy of the ketogenic diet was assessed among pediatric epileptic patients by application of a rigorous statistical meta-analysis. Nineteen studies from 392 abstracts met the inclusion criteria. The sample size was 1084 patients (mean age at initiation 5.78 ± 3.43 years). The pooled odds ratio, using a random effects model, of treatment success (> 50% seizure reduction) among patients staying on the diet relative to those discontinuing the diet was 2.25 (95% confidence interval = 1.69–2.98). The reasons for diet discontinuation included < 50% seizure reduction (47.0%), diet restrictiveness (16.4%), and incurrent illness or diet side effects (13.2%). The results indicate that children with generalized seizures and patients who respond with > 50% seizure reduction within 3 months tend to remain on the diet longer. Although no class I or II studies have been published regarding the efficacy of the ketogenic diet, this meta-analysis shows that current observational studies reporting on the therapeutic effect of the ketogenic diet contain valuable statistical data. Future observational studies should aim for long-term follow-up, patient dropout analysis, and improved seizure type characterization. (*J Child Neurol* 2006;21:193–198; DOI 10.2310/7010.2006.00044).

The ketogenic diet is an alternative treatment for intractable epilepsy, involving a strict regimen of high-fat, low-carbohydrate, and low-protein foods. It is used predominantly in children whose seizures have reached the refractory stage.[1,2] The diet is rigid and requires careful adherence but has been purported to show high success rates. Efficacy studies of the ketogenic diet are all observationally based and are often focused on patients able to remain on the diet for extended periods of time. Success rates primarily reflect outcomes in these individuals. However, most studies have large numbers of dropouts, making any analysis of true success challenging. This is complicated by the fact that the primary reason families give for discontinuing the diet is failure to achieve improved seizure control.[3] As such, improvement in seizure control is a key outcome directly affecting diet compliance. Analysis of response to therapy based primarily on patients persisting with the diet is, by definition, biased toward a positive appraisal of diet efficacy.

In this article, we use existing studies to systematically investigate diet effectiveness among patients who choose to remain on the diet in comparison with those who do not follow through with treatment. Specifically, the study (1) provides a systematic literature review of patient characteristics for those who continue or stop treatment, (2) summarizes data from individual studies using a random effects meta-analysis, and (3) assesses the quality of available studies of the ketogenic diet.

To our knowledge, this article is the first to apply a formal, conservative statistical meta-analysis to existing studies reporting on the use of the ketogenic diet for the treatment of epileptic seizures in children.

METHODS

Literature Search

Primary articles involving the ketogenic diet were extracted from a pediatric epilepsy article database created from an ongoing study conducted at

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the University of Utah.[4] This database was created from an exhaustive search using several interfaces assessing all medical literature dealing with pediatric seizures and epilepsy from 1980 to 2002.[4] An additional *MEDLINE* search of the literature was performed using *PubMed*, including years 1970 through 2003. The term "ketogenic diet" was paired with the medical subject heading (MESH) key words "ketosis" and "ketone," as well as each of the following terms: "epilepsy," "seizures," "focal seizures," "seizure type," "children," "refractory seizures," "generalized seizures," and "adolescents." Finally, the reference list of each of the primary articles reviewed above was examined for additional pertinent studies potentially appropriate for inclusion in this meta-analysis. Once combined, the above searches resulted in 392 articles to be evaluated.

Article Selection

Article selection was limited to primary research articles. Non-English articles, small case series and review articles were excluded, as were articles focusing on nonclinical aspects of the ketogenic diet. Studies of adult patients were also excluded. However, some articles that included adult and pediatric patients were retained because in all instances the majority of the subjects in these were under 18 years of age. To be included, the article had to have extractable data for patients who remained on the diet and for those who ceased following the diet at specific reported follow-up time points, including the numbers of subjects, patients achieving success, patients acquiring partial benefit, and patients with no change in seizure frequency at each recorded follow-up. Patient age, seizure types, and, when relevant, dropout information were recorded.

Definitions

For the purposes of the meta-analysis, therapeutic success was defined as ≥ 50% seizure reduction at follow-up. Conversely, patients experiencing < 50% seizure reduction at follow-up were considered not to have achieved therapeutic benefit.

Quality Assessment

Ketogenic diet studies included in this meta-analysis were rated for strength of evidence by one of three pediatric neurologists. The rating scheme (class I–IV) (Appendix) was adapted from Hirtz et al.[5] This is a standard classification scheme for treatment studies adopted by the American Academy of Neurology, the Child Neurology Society, and the American Epilepsy Society.

Meta-analysis of Diet Efficacy

We analyzed all available published evidence to determine the overall efficacy of the ketogenic diet. Studies included in this analysis reported the number of patients achieving success on the diet among two groups: those who continued to follow the diet up to a given time point (referred to as adherers) and those who ceased following the diet prior to this given time point (referred to as dropouts). (Note that a given individual could be counted as an adherer at the 6-month follow-up but as a dropout at a subsequent time point.) For each study, an odds ratio for each follow-up time point was computed for the success rate among patients remaining on the diet (adherers) versus the success rate among those discontinuing treatment (dropouts). A pooled odds ratio was calculated using the DerSimonian and Laird version of the random effects model[6] to determine whether patients remaining on the diet were more likely to have achieved success than those discontinuing the diet. A chi-square test for the effects of heterogeneity among the included studies was conducted. A P value < .05 was considered significant.

Diet Efficacy Over Time

Studies were pooled to explore trends in diet efficacy at 6, 12, and 24 months. To be included in this portion of the analysis, studies needed to provide data regarding the clinical response to the diet at one or more of these time points. Analysis compared diet efficacy in adherers versus dropouts. In addition, for those studies in which data were available, the rates at which children achieved 100% or > 90% seizure control were also recorded.

Summary Statistics

Summary statistics were used to determine significant effects of demographic differences and seizure control among adherers and dropouts.

RESULTS

Included Studies

Nineteen studies met the inclusion criteria.[7–25] The sample size was 1084 patients. The mean age of the sample was 5.78 ± 3.43 years (range 0.2–29 years). Included studies are summarized in Table 1.

Excluded Studies

Forty-three reviewed studies were excluded. The reasons for exclusion included the following: multiple studies involving the same population, outcomes not adequately specified, study duration of less than 30 days, studies not involving humans, review studies, and studies not relating to the outcome of treatment with the ketogenic diet.

Efficacy Analysis

For each study with adequate data, the rate of success among adherers and dropouts was calculated. Odds ratios for the 11 studies included in the meta-analysis are summarized in Table 2. A pooled odds ratio of 2.24 was obtained (95% confidence interval = 1.69 –2.98), indicating that patients remaining on the diet (adherers) were overall more than 2 times more likely to have achieved success with the diet than were those who ceased following the diet (see Discussion). The test for heterogeneity was insignificant (P = .347).

Efficacy Over Time

Data from 13 articles were summarized to determine the efficacy of the diet at 6, 12, and 24 months (n = 860). Figure 1 illustrates the rate of adherence to the diet as a function of time. Of the patients adhering to the diet (n = 422), 83.6% achieved success. The 24-month follow-up of patients on the diet in relation to seizure reduction is shown in Figure 2. In addition, of those remaining on the diet (for variable periods of time), overall 24% and 52% were reported to have achieved complete seizure control and ≥ 90% seizure control, respectively (see Table 2). (Note that the figure for ≥ 90% efficacy includes those with complete seizure control.)

Of the 1084 patients from all 19 studies, 552 (50.9%) became dropouts at various time points. The reasons for dropping out of the diet are listed in Table 3.

Other Factors Influencing Adherence or Dropout Rates

The rate of patient adherence was compared to dropout based on age and seizure type. Despite the constraints imposed by limited data, there was a significant effect of seizure type on treatment efficacy (P < .005), with children experiencing generalized seizures, infantile spasms, and multiple seizure types responding better

Table 1. Included Studies

Study	Study Type	Year	Subjects (Total)	Duration (mo)*	Males	Age (yr) Mean (Range)	Diet Type	Strength of Evidence†
Hopkins and Lynch[7]	Prospective	1970	34	24	—	(1.0–12.0)	CD	IV
Sills et al[8]	Prospective	1986	50	24	—	—	MCT	IV
Woody et al[9]	Prospective	1988	15	24	—	2.4 (1.7–8.0)	MCT	IV
Vining et al[10]	Prospective	1998	51	6	34	4.7 (1.3–8.6)	CD	III
Freeman et al[11]	Prospective	1998	150	48	85	(0.3–16.0)	CD	III
MacCracken and Scalisi[12]	Prospective	1999	11	36	—	4.8 (1.0–12.6)	CD	IV
Kankirawatana et al[13]	Prospective	2001	35	12	16	5.4 (0.2–12.0)	CD/MCT	III
Lightstone et al[14]	Prospective	2001	46	6	26	5.3 (0.4–16.5)	CD	IV
Vining et al[15]	Prospective	2002	237	12	130	3.7 (0.2–9.8)	CD	III
Coppola et al[16]	Prospective	2002	56	18	36	10.4 (1.0–23.0)	CD	III
Trauner[17]	Retrospective	1985	17	—	10	(1.0–13.0)	MCT	IV
Hassan et al[18]	Retrospective	1999	52	—	27	5.5	CD/MCT	III
Couch et al[19]	Retrospective	1999	26	—	11	4.4 (2.0–11.0)	CD	III
Maydell et al[20]	Retrospective	2001	143	12	87	7.5 (0.3–29.0)	CD	III
Nordli et al[21]	Retrospective	2001	31	—	18	1.2	CD	III
Wirrell et al[22]	Retrospective	2002	14	—	—	7.3 (1.0–16.8)	CD	IV
DiMario and Holland[23]	Retrospective	2002	48	12	16	6.5 (1.0–15.0)	CD	III
Kossoff et al[24]	Retrospective	2002	23	—	17	1.1 (0.4–2.0)	CD	III
Mady et al[25]	Retrospective	2003	45	—	25	14.4	CD	III

CD = classic diet; MCT = medium-chain triglyceride.
*Total months on diet.
†Class I–IV based on a standard classification scheme for treatment studies (see Appendix).[5]

(Table 4). The weighted mean age among patients adhering was 5.41 ± 1.08 years and among patients who dropped out was 9.06 ± 4.88 years (P = .209). The mean duration on the diet among adherers was 8.08 ± 5.24 months. The following represented the most frequently reported side effects among patients remaining on the diet for at least 3 months: constipation (14%), weight loss, growth problems, or anorexia (13%); nausea and vomiting (5%); behavioral problems or irritability (4%); increased serum cholesterol or triglycerides (4%); lethargy (4%); hypercalciuria (2.5%); increased liver enzymes (2.4%); renal stones (1.9%); and diarrhea (1.6%). Hypoglycemia was reported only in 1.3%. (These values represent the number of side effects occurring in all studies as a percentage of patients remaining on the diet for at least 3 months.) It was not possible to determine the relative rates of these side effects among subjects discontinuing the diet. Nine deaths were reported, of which eight were judged "unrelated" to the diet.

Quality Assessment

All 19 studies were rated as either class III or class IV. In general, to warrant a class I or II rating, a therapeutic study must compare a treatment group with a distinct control group. If a patient acts as his or her own control (as pertains to all of the studies of ketogenic diet efficacy included herein), then the study, by definition, is at best a class III study (see Discussion).

Table 2. Measurement of Response in Individual Studies

Study	Year	N*	Number (%) Achieving Success on Diet		OR (95% CI)	No. Seizure Free, n/N (%)§	> 90% Reduction n/N(%)§
			Adherers, n/N (%)†	Dropouts, n/N (%)‡			
Hopkins and Lynch[7]	1970	34	8/19 (42)	2/15 (13)	3.16 (0.58–17.13)	3/19 (16)	NR
Vining et al[10]	1998	51	20/24 (83)	5/23 (22)	3.83 (1.23–11.92)	5/24 (21)	11/24 (46)
Freeman et al[11]	1998	150	75/83 (90)	19/65 (29)	3.09 (1.70–5.63)	11/83 (13)	NR
Kankirawatana et al[13]	2001	35	10/12 (83)	2/10 (20)	4.17 (0.74–23.61)	3/12 (25)	8/12 (67)
Vining et al[15]	2002	237	115/135 (85)	57/99 (58)	1.48 (0.98–2.23)	34/135 (25)	71/135 (53)
Coppola et al[16]	2002	56	4/5 (80)	4/51 (8)	10.20 (1.93–53.79)	0/5 (0)	NR
Trauner[17]	1985	17	7/9 (78)	3/8 (38)	2.07 (0.40–10.84)	5/9 (56)	NR
Maydell et al[20]	2001	143	54/64 (84)	22/64 (34)	2.45 (1.34–4.49)	23/64 (36)	38/64 (59)
Hassan et al[18]	1999	52	7/7 (100)	28/44 (64)	1.57 (0.50–4.96)	NR	NR
Kossoff et al[24]	2002	23	13/13 (100)	8/10 (80)	1.25 (0.37–4.18)	3/13 (23)	6/13 (46)
Mady et al[25]	2003	45	13/20 (65)	6/25 (24)	2.71 (0.87–8.40)	NR	6/20 (30)

CI = confidence interval; NR = not reported; OR = odds ratio.
*Total patients initially entered into the study.
†Number of patients achieving success (n) among the total number (N) of patients remaining on the diet at the end point (%).
‡Number of patients achieving success (n) among the total number (N) of patients discontinuing the diet at the end point (%).
§Number (n) of patients among those remaining on the diet (N) who achieved complete or ≥ 90% reduction in seizure frequency, respectively. The 90% reduction column includes those with complete seizure control.

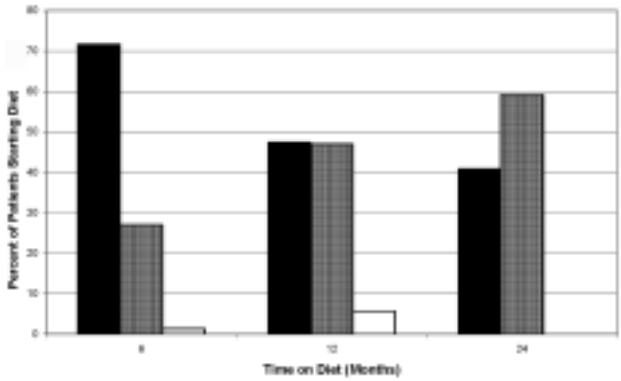

Figure 1. Continuation of the ketogenic diet over time. The percentage of patients remaining on the diet at specific follow-up time points (in months) (solid bars), the percentage having discontinued the diet (hatched bars), and the percentage missing or lost to follow-up (open bars) are shown.

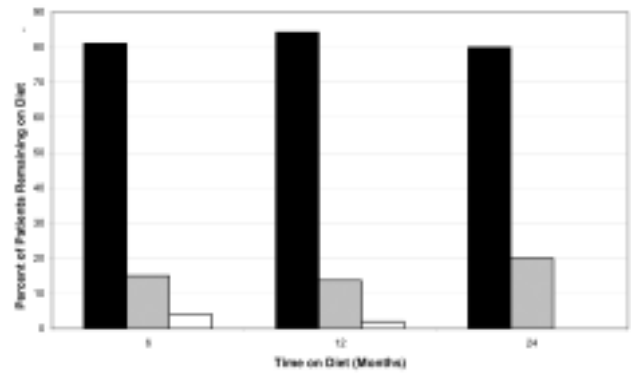

Figure 2. Therapeutic success among patients remaining on the ketogenic diet. The percentage of patients achieving success (> 50% reduction in seizure frequency) among those remaining on the diet at each follow-up time point (in months) (solid bars), the percentage with less than 50% control (hatched bars), and the percentage missing or lost to follow-up (open bars) are shown.

DISCUSSION

This article is not the first to summarize existing published studies of the ketogenic diet in an effort to better assess the therapeutic efficacy of this treatment modality when applied to children with epilepsy. Several excellent reviews of this treatment exist, some published quite recently.[2,3,26,27] However, our approach complements these studies insofar as it applies a rigorous statistical method in an attempt to quantitatively define the efficacy of this treatment.

Application of this method demonstrates that patients remaining on the diet are statistically more likely to have achieved therapeutic success (> 50% reduction in seizure frequency) than are those ultimately discontinuing the diet (by a factor of 2). Presumably, this is because patients benefiting from the diet in terms of improved seizure control are more likely to remain on the diet. However, the disparate means of reporting data, the variable time points reported by the included studies, and the variability with which published studies deal with children discontinuing the diet make it impossible to absolutely prove this logical assumption. Nevertheless, the result provides formal statistical and quantitative support for the now widespread impression that the ketogenic diet is, in fact, efficacious in the treatment of pediatric epilepsy. This conclusion is further supported by the remarkably high percentage of patients reported as having achieved complete seizure control or ≥ 90% seizure reduction (24% and 52% of adherers, respectively).

Our findings suggest that patients with generalized seizures show the most consistent positive response to the ketogenic diet. These findings are similar to those of previously published studies. Maydell et al reported that more patients with generalized seizures responded favorably to the diet compared with patients with focal seizures.[20] Seventy-three percent of their patients with focal seizures dropped out of the study compared with 45% of the patients with generalized seizures. Our inability to identify any additional significant differences in efficacy based on seizure or epilepsy type is due to small samples and insufficient detail in reporting.

Although our meta-analysis indicates that patients remaining on the diet tend to be younger than those discontinuing it, this difference was not statistically significant. In other studies, age does appear to influence the clinician's decision regarding institution of the diet. Studies have found that seizure reduction was most likely in those who had experienced seizures for the shortest period of time before diet initiation. Furthermore, difficulty accepting dietary restrictions appears to be higher among adolescents, presumably affecting compliance with the diet.[16,25,28] Given the mean age of 5.78 ± 3.43 years of our pooled sample, it is apparent that the majority of patients treated with this modality are younger. Our findings support the suggestion of Lightstone et al that more children are needed in the > 12 years age group to provide a better understanding of diet discontinuation in adolescents.[14]

The initial 3 months on the diet are typically considered a trial period. If a child achieves success by the end of this time period, long-term success on the diet is more likely. For example, Vining et al reported that 71% of patients with 50% seizure control at 3 months stayed on the diet through 12 months.[10] However, most studies lack quality data for follow-up beyond 12 months. Three of the included studies report data for patients between 12 and 24 months[7,9,24]; three additional studies report data after 24 months.[11,17,25] The inconsistency of long-term follow-up is gen-

Table 3. Reasons for Diet Discontinuation

Reasons for Diet Discontinuation (Reasons for Dropping Out)	n	% of Total Dropouts
Ineffective	259	46.9
Too restrictive	60	10.9
Illness/side effects	88	15.9
Poor compliance	47	8.5
Other plus lost to follow-up	98	17.8

Table 4. Effect of Seizure Type on Diet Continuation

Seizure Category	Adherers, n (%)	Dropouts, n (%)
Generalized seizures	133 (16.7)	74 (13.0)
Nongeneralized seizures	33 (4.1)	34 (6.0)
Infantile spasms	21 (2.6)	5 (0.9)
Multiple seizure types	66 (8.3)	6 (1.1)

erally insufficient to quantify diet discontinuation after longer treatment intervals. Of note, some patients discontinued the diet after prolonged (> 12 months) treatment periods after achieving an apparent remission (presumably no longer requiring treatment for epilepsy). More long-term studies are needed to determine the relative rates of relapse versus remission in individuals choosing to discontinue the diet after 12 to 24 months of treatment.

Our results also demonstrate that despite considerable attention and clinical use internationally, studies investigating the efficacy of the ketogenic diet in the treatment of pediatric epilepsy do not meet class I or class II standards. This, however, is clearly due to the likely insurmountable obstacles inherent in the conduction of blinded, controlled studies of its therapeutic efficacy. According to published criteria for evidence-based assessments of therapeutic investigations,[6] class I and II investigations require blinded comparison of an experimental treatment with an appropriate control group. Any study employing a treatment group as its own control can, by definition, achieve only class III status at best. Class III articles are considered of only "moderate" quality. Without supporting class I or II studies, numerous coincident class III studies are required to justify specific clinical recommendations as a consequence. The statistical analysis applied here confirms that this circumstance in fact applies to the existing body of class III studies assessing the efficacy of the ketogenic diet. The calculated odds ratio is significant, clearly indicating benefit, and the test for heterogeneity (insignificant with $P = .347$) indicates that the preponderance of individual studies contributed to this positive conclusion.

Other authorities on the ketogenic diet have discussed the serious methodologic difficulties that are likely to preclude investigators from accomplishing class I or II studies for this particular therapeutic modality.[3,29] Clearly, blinded randomization of subjects to the ketogenic diet versus another, less restrictive diet would be incredibly challenging if not impossible. The difficulty of preparing the diet (for families) and of administering and monitoring the children (for medical professionals) clearly interferes with the possibility of blinded treatment. Furthermore, the large collection of class III evidence supporting efficacy (confirmed as well by our results) suggests that randomized comparison with a likely ineffective "regular" diet might be unethical. Recent suggestions that a modification of the Atkins diet might prove effective in the treatment of epilepsy indicate that one alternative could perhaps involve "blinded" randomization to the standard ketogenic diet versus the less restrictive Atkins diet.[27,30]

A Cochrane Review on this subject recommended open, randomized, parallel trials including control treatments combining sham diets with best medical treatment.[29] Freeman and Vining, on the other hand, have designed a trial involving a double-blind, placebo-controlled, crossover study of the efficacy of the ketogenic diet in the control of frequent atonic and myoclonic seizures.[31] The inclusion in the child's dietary regimen of a "Kool-Aid-like drink" containing saccharine with or without glucose allows for maintenance of ketosis in a blinded, crossover fashion. Evaluation of efficacy is based on seizure counts and on the frequency of electrographically identified seizures. Although this study evaluates the short-term efficacy of the ketogenic diet in a blinded fashion, it probably would not allow for blinded evaluation of long-term benefit.

Recognizing that randomized, controlled trials of the ketogenic diet can be difficult to achieve, certain methodologic problems common to many existing studies could perhaps be improved in future investigations. Outcome analyses are disparate between studies, and long-term follow-up is limited. Many studies provide little information regarding seizure type, and few define epilepsy type using the standard International Classification of the Epilepsies.[32] Finally, analysis of the dropouts is often unsatisfactory, leading to an inability to determine clearly a priori the clinical characteristics of those individuals likely to stop the diet from lack of efficacy. Our study, along with others, clearly suggests that individuals are more likely to remain on the diet if they benefit from it in terms of reduction in seizure frequency. Therefore, it might be as important to carefully assess the nature of children "giving up" the diet as it is to evaluate those remaining on the diet for longer periods of time.

CONCLUSIONS

This meta-analysis provides formal statistical support for the efficacy of the ketogenic diet in the treatment of epileptic children. Data indicate that children remaining on the diet for more than 3 months have approximately a twofold chance of sustaining improved seizure control. Children with generalized seizures have a greater chance of obtaining both improved seizure control and/or antiepileptic drug reduction. There is a tendency for younger children to adhere to the diet more consistently than adolescents, although this trend was not statistically significant. Taken together, existing studies provide valuable statistical evidence supporting the ketogenic diet. Although future double-blind, controlled studies might be desirable, such investigations might, realistically, be very difficult to achieve. Ideally, future studies could be improved by providing longer follow-up of successful patients, better defining the clinical characteristics of children not benefiting from the diet, and further characterizing outcome differences stratified by seizure and epilepsy type.

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Appendix. Evidence Classification Scheme for Therapeutic Studies

Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population. The following are required: (a) primary outcome(s) clearly defined; (b) exclusion/inclusion criteria 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 are 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 criterion, 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 from uncontrolled studies, case series, reports, or opinions.

Adapted from Hirtz D et al.[5]