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Review Article

A Systematic Review of the Use of the Ketogenic Diet in Childhood Epilepsy

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The ketogenic diet has been used in the treatment of intractable childhood epilepsy since the 1920s. A systematic review of the efficacy, adverse reactions, and costs associated with using the diet was performed. PubMed and Ovid searches were performed using the keywords epilepsy/therapy, dietary therapy, ketogenic diet, adverse events, and costs. Cochrane library was searched. Bibliographies of papers located by searches and review articles were compiled. Papers published after 1990 were selected if they were written in either English or French and reported on the use of classic ketogenic diet in patients under age 18 years of age with medically refractory epilepsy. Outcome measures were degree of seizure control, duration patient remained on diet, and occurrence of adverse events. Twenty-six studies were found. No prospective-controlled studies were found. Fourteen studies met all criteria for inclusion. The studies indicated that some children report reduction in seizure frequency. The estimated rate for obtaining complete seizure control was 15.6% (95% confidence interval 10.4-20.8%) with 33% (95% confidence interval 24.3-41.8%) reporting greater than 50% reduction in seizures. Adverse events were not frequent; however, 16 cases of death occurring while on the diet were found. No cost/benefit studies were located. There is evidence to support the cautious use of ketogenic diet in children with refractory epilepsy

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Introduction

Fasting has been used in the treatment of epilepsy since Biblical times (Matthew 17:5-21). The first modern reports of its use in the medical literature were by Guelpha in 1911 and Conklin in 1921 [1]. Their hypothesis was that prolonged fasting resulted in detoxification of the gut, resulting in a decrease in the frequency of seizure occurrence. In 1921, Wilder postulated that the antiepileptic effect of the diet was related to the production of ketones and not to starvation [1]. He proposed that increasing the fat content in the diet while reducing the carbohydrate would lead to reduction in seizure frequency. Based on Wilder's hypothesis, Talbot in 1927 developed a ketogenic diet protocol similar to present-day diet which consisted of a period of fasting followed by the introduction of a 4:1 fat to carbohydrate ratio diet in association with restriction in water intake [1]. With the development of newer antiepileptic drugs with improved efficacy and convenience, there was a significant decrease in the use of the ketogenic diet until recently. With the publicity in the lay press of the case of "Charlie" in 1994, a renewed interest and popularity of the diet has occurred. Several studies since that time have suggested that the diet could be an effective alternative to treatment for children with refractory epilepsy [1]. The purpose of this paper was to review the evidence in the medical literature for the efficacy, safety, and cost of treating a child with the classic form of the ketogenic diet.

Methods

Method of Search

A search of the medical literature databases PubMed and Ovid was performed using the keywords "epilepsy/therapy" cross-referenced with

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the text word "ketogenic diet", followed by using the keyword "dietary therapy" cross-referenced to text word "epilepsy". Search for reported adverse reactions while on the ketogenic diet was performed using the same database with keyword "epilepsy" cross-referenced to "toxicity/adverse results" followed by "ketogenic diet". Search for the cost of treatment using the ketogenic diet was performed using the same database using the keyword "epilepsy/therapy " with text word "cost benefit" followed by "ketogenic diet".

The Cochrane library of clinical trials was searched for the term "ketogenic diet". Bibliographies of all articles retrieved by the searches were reviewed for missing reference citations.

Selection and Analysis of Studies

Review of the bibliographies and searches revealed references dating to 1920. Because of differences in methods reported and types of diet being used in the earlier literature, articles review was limited to those articles published after 1990. Papers written in either English or French that reported on the outcome after using the classic ketogenic diet to treat patients with refractory epilepsy and who were under the age of 18 years at the time of commencing the diet were included in the initial review. Refractory epilepsy was defined as suboptimal control of seizures despite use of multiple antiepileptic medications.

Papers were reviewed to obtain information as to type of study (prospective blinded study, prospective nonblinded study, retrospective or case report), description of patient population (age, seizure types, duration of seizures before medication, and medications being used), sample size, outcome with regard to seizures control, tolerability of diet (length of time remains on diet), toxicity/adverse reaction. Based on this information, the papers were then classified as to degree of evidence each paper offered. Class One Evidence consisted of a prospective-controlled study with well-defined cohort, adequate sample size, blinded interpretation of outcome, and in which a description of method of analysis used was present. Class Two Evidence was either an uncontrolled prospective study or a retrospective study which had well-defined cohort, an adequate sample size, blinded interruption of outcome, and a description of method of analysis used. Papers not meeting either of these sets of criteria were classified as Class Three Evidence. Review articles by experts or expert consensus articles were included in this group.

The principal outcome measure used for the present review was the degree of decrease in seizure frequency during that time. Optimal outcome was when there had been complete cessation of seizures. A seizure reduction of 50% or greater was considered a clinically significant decrease. For this review, the time period used to determine degree of seizure freedom was arbitrarily chosen as 6 months after beginning the diet. Tolerance of the diet was assessed by the length of time the patient remained on the diet. Using the intent to treat, the percentages of patients obtaining the outcome measure for each study were obtained. Combined analysis of the percentages of patients achieving the relevant outcome measure was performed using the confidence profile method to evaluate the overall outcome.

Papers reporting adverse events at any time after commencing the ketogenic diet were searched for information regarding patient demographics (sex, age, duration of seizure disorder, seizure type, comedication, associated diagnosis), timing of event in relationship to initiating the diet, duration of symptoms, whether hospitalization occurred as a result, or in case of already hospitalized patient, whether hospitalization had been prolonged as a result of the occurrence. For this study, an adverse event was defined as any event, expected or otherwise, that occurred to the patient while on the diet. The adverse event was classified as significant or life-threatening if it resulted in hospitalization or prolongation of hospital stay or if death occurred while on the diet. Cases of reported deaths were examined separately.

Papers reporting on the cost/benefits of the use of the ketogenic diet had to address the following points to have been considered. There had to have been a clear group comparison using similar groups of patients on and off diet. Clear outcome measures had to have been defined. All costs, real and economic, not just accounting costs had to have been provided. All costs had to have been weighed against each other. Papers meeting these criteria, and demonstrating that in providing the diet the benefits outweighed the costs, were accepted as supporting the hypothesis that the ketogenic was cost-efficient for both caregivers and health care providers.

Results

Efficacy of the Ketogenic Diet

Since 1990, a total of 26 studies were identified that meet the above stated criteria [2-28]. No papers met the criteria for Class One Evidence. Seventeen papers met the criteria for Class Two Evidence [2-19]; however, three of these papers were excluded as clinical assessment of seizure control was made at less than 6 months after initiating diet [17-19]. Two papers reported on studies performed in a prospective nonblinded fashion using a fixed study protocol [9,10]. The remaining studies were retrospective (Table 1). Nine papers consisting of reviews or expert's opinion were classified as Class Three Evidence [20-28]. Papers classified as Class One or Two Evidence were included in the analysis of efficacy of the diet.

In the studies meeting all criteria for inclusion, the total collective patient population was 972. Information as to seizure types was difficult to obtain, as a standard classification system was not used across the papers and many patients were reported to have had more than one seizure type. All patients had been on multiple antiepileptic medications before commencing the diet. At 6 months an average of 15.6% (95% confidence interval [CI] 10.4-20.8%) of the patients had become seizure-free, while 33.0% (95% CI 24.3-41.8%) were reported to have achieved greater than 50% reduction in seizure frequency after commencing the diet (Table 1). The variation of the amount of demographic information and lack of uniformity of its presentation between papers prevented an assessment of factors which might predict which patients would be more likely to respond to the diet.

Ten of the 15 papers had sufficient data to determine the length of time each patient had remained on the diet (Table 2). For the group, 79.9% (95% CI 72.3-87.5%) of the patients were able to remain on the diet for at least 3 months, 60.6% (95% CI 50.3-70.9) remained for 6 months, and 35% (95% CI 21.6-48.4%) for a year or more. Information as to why patients discontinued the diet was often not clearly mentioned. However, when mentioned, the most frequently cited reasons were lack of efficacy of the diet and compliance. Side effects were not commonly cited as the reason.

Reporting of Adverse Events While on Ketogenic Diet

The search located 27 papers, which included a list of adverse events that occurred while patients were on the diet [2-18,22,25,26,29-36]. None of the papers met the

Table 1. Efficacy of ketogenic diet 6 months after initiation

Author	Diet Fast	Design	Total Sample	% Sample at 6 Months	% Seizure -Free*	% Greater Than 50% Reduction*
DiMario [2]	y	R	48	50	8	35
Coppola [3]	y	R	56	38	7	20
Maydell [4]	y	R	146	66	16	12
Hassan [5]	y	R	53	39	11	26
Kankirawatana [6]	y	R	35	57	17	40
Kang [7]	y	R	199	61	33	58
Nordli [8]	y	R	32	66	19	22
Vining [9]	y	P	51	69	12	53
Freeman [10]	y	P	150	77	3	51
Kossoff [11]	y	R	23	78	17	55
Kinsman [12]	y	R	58	?	29	38
Ruthenstein [13]	y	R	13	77	6	15
Lion François [14]	y	R	29	?	10	35
Wirrell [15]	n	R	14	86	14	14
Vaisleib [16]	n	R	65	100	32	22

Abbreviations:
N = No fast
P = Prospective -no control group
R = Retrospective
Y = Fast present
* Percentage based on initial sample size (intent to treat).

criteria for Class One Evidence. Eighteen papers met the criteria for Class Two Evidence [2-18,29], and 10 papers [22,25,26,30-36] described small case series or individual case reports (Class Three Evidence). The latter group was included in the tabulation of frequency of side effects (Table 3) if there was an indication of the population from which the case series were drawn. Single case reports were otherwise not included.

Adverse events in the series were relatively infrequent, with vomiting and elevated serum lipid levels being the most common (Table 3). It was not possible to ascertain whether a patient had one or more adverse reactions on the diet. Most papers did not include demographic information about the patient who had the event. Thus it was not possible to determine which person was at greater risk of developing an adverse reaction after commencing the diet.

As well, determination of the degree of severity of the adverse events was difficult, as information as to whether the adverse event resulted in prolonged hospitalization or if the diet led to the discontinuation of the diet was not included in the reports. Deaths were reported in 16 patients while on the diet [4,5,7,8,10]. Table 4 lists the causes of the deaths. Again, sufficient demographic information was not usually reported in the case series. There were two additional case reports of death while on ketogenic diet—one secondary to pancreatitis [35] and another in association with propofol infusion syndrome [36]. As these two cases were case reports, they were not included in the tabulation of the frequency of reported adverse events as reported in Tables 3 and 4.

Table 2. Time patient remains on ketogenic diet

Author	Total Sample	% Sample at 3 Months	% Sample at 6 Months	% Sample at 12 Months
DiMario [2]	48	?	50	37
Coppola [3]	56	75	38	7
Maydell [4]	147	80	66	48
Hassan [5]	52	68	39	13
Kankirawatana [6]	35	62	57	12
Kang [7]	199	88	61	27
Vining [9]	51	88	69	47
Freeman [10]	150	83	71	55
Ruthenstein [13]	13	85	77	50
Kossoff [11]	23	91	78	56

Table 3. Adverse events reported while on ketogenic diet

Side Effect	Number of Cases (n = 1066)	% of Total Sample
Vomiting	59	5.53
Increase serum lipid levels	28	2.63
Acidosis	20	1.88
Increased serum uric acid	19	1.78
Gastric (diarrhea/constipation)	20	1.88
Renal stones	12	1.33
Hypoglycemia	9	0.84
Increased rate of infections	8	0.75
Gallstone formation	4	0.38
Dehydration	3	0.28
Significant elevation of liver enzymes	2	0.19
Protein loss enteropathy	2	0.19
Pancreatitis	1	0.09
Deaths	16	1.50

Table 4. List of the causes of death as reported in series

Cause of Death	Number of Reported Cases
Infection	3
Lipoid pneumonia	3
Cardiac arrest	2*
Respiratory arrest	2
Status epilepticus	2
Gastric hemorrhage	1
Metabolic failure	1*

* One patient's diagnosis pyruvate dehydrogenase deficiency for each cause.

Reports of the Cost/Benefit Analysis of Diet

The literature search failed to find papers that met inclusion criteria for this review. Gilbert et al. [37] reported a 67% reduction in the cost of co-medications in children who managed to remain on the diet for over 1 year. Other costs were not examined in this paper.

Discussion

To establish the efficacy of a new antiepileptic agent for marketing, it must be demonstrated to decrease the frequency of seizures more than the control in a safe manner [38]. This procedure requires the development of a blinded prospective study using a well-defined cohort and sufficient sample size to demonstrate efficacy of the agent (i.e., Class One Evidence). To date, no studies met the criteria for Class One Evidence for efficacy in the use of ketogenic diet in children with refractory epilepsy.

The development of a blinded prospective trial of the ketogenic diet in children would be difficult to design [39]. Finding a placebo with similar metabolic responses to the diet at the time of initiation (i.e., acidosis, lethargy, hypoglycemia) and during maintenance (presence of ketones) that does not have antiepileptic properties would be difficult. In addition, as the child's caregiver prepares and administers the diet over a protracted period of time, it would be difficult to ensure that the caregiver had no knowledge of the ketogenic diet, especially with the ease of access to information about the diet from the Internet.

To overcome these difficulties, head-to-head randomized studies comparing the diet with active control (i.e., Atkins diet [40] or other antiepileptic drug) have been suggested [39]. This type of study might be able to prove valuable information, but might not provide reliable evidence of the effectiveness of the diet [41]. Prior placebo-controlled studies of the control agent in the same study population using a similar protocol are necessary for comparison. To date, this information is not readily available for this patient population.

There were, however, several studies that did supply Class Two Evidence supporting the efficacy of the diet. These papers reported an overall reduction of seizure frequency greater than 50% in approximately one third of children initiated on the diet. The duration the child remained on the diet was variable, with over half the children discontinuing the diet between 6 months and a year after onset of treatment. Because of the variation in study designs and in the description of the clinical variables (such as seizure type, electroencephalographic findings, duration of treatment), it was not possible to assess which child might benefit most from the diet.

Though side effects were infrequently reported to have occurred while patients were on the diet, the death of 16 children while on the diet is concerning. Information about each case was limited; therefore, it was not possible to make a definite statement of cause and effect. The occurrence of the deaths suggests that caution and careful supervision of the patient while on the diet by an experienced dietitian and neurologist is necessary. In patients with cardiac arrhythmias such as prolonged QT interval [42], and in patients with underlying metabolic disorders or those taking zonisamide, topiramate, or acetazolamide [43,44], the use of the diet might be associated with a higher risk of adverse events.

The question of the cost/benefit ratio for the diet remains unanswered. The study of Gilbert et al. [37] reported that there was a significantly decreased cost in medications while on the diet. This study was not a cost/benefit analysis [45]. The calculation of costs was based only on drug costs. The indirect costs of lost earnings of the caregiver while learning the diet, in the preparation of the diet, and during visits to health professionals were not included. The direct costs of biochemical tests necessary while on the diet, medical visits, equipment necessary for the diet, vitamin supplementation, and hospitalization were also not included. The selection of a small group of patients who remained on the diet for a year rather than all patients who began the diet in order to calculate the cost of the reduction of medication introduces a significant bias in the calculation of costs.

Though there is Class Two Evidence supporting the continued use of the ketogenic diet in children with refractory seizure disorders, questions still remain to be answered: which patient would benefit most by commencing the diet, what type of diet is best, how long to remain on the diet, which patient is at risk of an adverse event, and is there a cost/benefit of the diet. To answer these questions, a series of national multicenter prospective studies, using a well-defined cohort of patents and building on previous results, is required.

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