Effectiveness of Ketogenic Diet in Children with Epileptic Disorders: A Meta-Analysis and Systematic Review

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ABSTRACT

Background: Epilepsy is a central nervous disorder that affects children at great magnitude. Cognitive, emotional, and behavioral symptoms are common. The ketogenic diet (KD) is a dietary treatment option, particularly for intractable seizures. The effectiveness of KD in the management of epileptic disorders (ED) varies between studies. Objective: The aim of this meta-analysis and systematic review is to determine the effectiveness of KD in the management of ED in children. Methods: A literature search was performed using relevant key terms to identify studies published from 1998 to 2017 on KD, ED, and children. Studies were identified through an electronic search of Embase, MEDLINE, and ProQuest databases. The main outcomes and measures were ≤50% reduction of seizure episodes at one month, three months, six months and twelve months of treatment. Data were pooled using random effects meta-analysis technique. Results: Fourteen studies were included in the meta-analysis and systematic review including 1276 participants. Reductions of seizure episodes by ≥50% (which is clinically relevant) using KD were 22.9%, 49.9%, 37.9% and 30.8% after one month, three months, six months and twelve months of treatment, respectively. Conclusion: There is some evidence that KD is effective in the management of some cases of ED. Reduction of ≥50% seizure episodes is seen mainly at the first three months and declines thereafter, possibly due to the side effects or non-adherence with KD. The decision to adopt this type of diet should be based on both short-term and long-term goals, taking into consideration the cost, safety and efficacy of the treatment. Effectiveness in the first three months appears to be an indicator of the outcomes of interest.

Keywords: Ketogenic Diet, Epileptic Disorder, Children, Meta-analysis, Systematic Review


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INTRODUCTION

Seizure is a sudden disruption of the brain’s normal electrical activity accompanied by altered consciousness and other neurological and behavioral manifestations (1). Epileptic disorders (ED) are a condition characterized by recurrent seizures that may include repetitive muscle jerking called convulsions and starts in childhood in more than half of the cases (2). Manifestations of this condition depend on the affected site of the brain, which could be sensory, motor, or autonomic functions, and can predispose to an aura in a certain type of epilepsy (3). Epilepsy is a multifactorial disease that leads to an imbalance between brain excitatory and inhibitory signals, of which about 70% is idiopathic, while other etiologic factors could be genetic, head trauma, neurologic diseases, or metabolic disorders (3). Laboratory studies such as a complete blood count, blood chemistry profiles, liver, and thyroid function tests, an electroencephalogram, and a brain study with magnetic resonance imaging are indicated for diagnosing epilepsy. Computed tomography scanning in an emergency or for very young children to help aiding the diagnosis (4).

The mainstay of treatment is antiepileptic drug (AED) therapy which has four aims: elimination of seizures or reduce their frequency to the maximum degree possible, to evade the adverse effects associated with long-term treatment, and to aid patients in maintaining or restoring their usual psychosocial and vocational activities and in maintaining a normal lifestyle (4). Seizures, including febrile convulsions, occur in 3-5% of children. Epilepsy, that is susceptibility to continuing seizures, occurs in 0.5-1.0% of the population and is intractable to current antiepileptic drug treatment in 20-25%. Intractable seizure is defined when the patient fails to manage his or her attack in the following situation: (i) failure reduction of attacks with the use of two types of anticonvulsant drugs, (ii) occurrence of average at least one seizure per month, (iii) three months or less free of seizure in a year (5).

The ketogenic diet (KD) is a type of therapeutic diet that is high in fat and low in carbohydrates. It aims to induce the metabolic effects of fasting. Many types of KD are used nowadays including classical ketogenic diet, the medium-chain triglycerides diet, the modified Atkins diet (MAD) and the low glycemic index diet. Possible mechanisms
of action of KD in epilepsy were summarized in a recent review: evidence suggest that carbohydrate reduction may contribute to the activation of ATP-sensitive potassium channels by mitochondrial metabolism, inhibition of glutamatergic excitatory synaptic transmission, inhibition of the mammalian target of rapamycin pathway (6). KD is suitable regime for children who have failed to manage their epilepsy episodes by using two to three antiepileptic therapy medications particularly those who suffered from generalized epilepsy, or those who have been referred to a tertiary pediatric epilepsy specialist. Regardless the effect of KD, it is contraindicated in children who have known case of pyruvate carboxylase deficiency, β-oxidation defects, primary carnitine deficiency and porphyria disorders (6). Clinicians observed multiple short-term side effects when initiating KD in pediatrics, including vomiting, anorexia, acidosis, constipation, gastro-esophageal reflux disease, fatigue, exacerbation of seizures and hypoglycemia. Long-term side effects may include vitamin D deficiency, increased risk of bone fractures by decrease bone mineral density, growth disturbance after age of 6-12 years, cardiovascular disease and kidney stones. Patients treated with KD need to undergo regular clinical visits upon the initiation of the diet and during treatment at three months, six months, twelve months for monitoring the therapeutic effect of the diet and the avoidance of side effects (6). Variable findings have been reported regarding the effectiveness of KD in treating and alleviating the symptoms of ED with variable treatment periods. Therefore, the aim of this meta-analysis and systematic review is to determine the effectiveness of KD in the management of ED in children.

METHODS
This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement as a guideline for reporting (7).

Databases searches: In January 2018, the authors conducted EMBASE, MEDLINE (via PubMed), ProQuest Medical and Google Scholar. The review team developed a list of search strategy, including terms ketogenic diet, epilepsy, seizures, epileptic disorders, seizure disorders, and children. Furthermore, the review team manually screened the
references of the found papers for potential inclusion in the review. English language and human studies were set as limits.

The authors included all studies that aimed to study the effectiveness of KD in children with ED. Included studies satisfied the following criteria: (i) they were published in the English language; (ii) published between 1998 and 2017, and (iii) the focus of the study was to examine the effectiveness of KD in children with ED. The outcome of interest was 50% reduction in seizure frequencies.

**Data synthesis and statistical analyses:** Two review authors independently assessed each study. The agreement was reached after panel discussion, and then eligibility was determined. For each study, the following data were extracted: study ID, year of study, country, study design, sample size, sample characteristics, age at start of the KD, main results/findings, and any other significant clinical notes.

The data were pooled in this meta-analysis using random-effects model using the DerSimonian-Laird method, reporting the pooled prevalence and corresponding 95% confidence interval. Data were presented using Forest plot. When two or more studies reported the same dataset, the first publication was included in the meta-analysis. An assessment of studies heterogeneity using the $\text{I}^2$ statistic was performed; the value $\geq 75\%$ was used to represent high heterogeneity.

**Ethical considerations:** As this review is a sort of secondary analysis aiming at assessing data from publications that are already indexed and available in the public domain, no ethical approval nor informed consent were applicable.

**RESULTS**

**Study characteristics:** As presented in Table 1, fourteen studies, accounting for 1276 participants in eight different countries were included in the analysis. Female participants were 42%. The age range was two months to eighteen years of age. The median age at the start of KD was 40 months of age (range 20-90 months), while the median number of AED used by participants were three AED (range 2-8 medications). The median number of participants per study was 49 (range 9-317). Five out of the fourteen studies used observational research design (mainly cohort design), and the remaining nine used experimental research design to report the effectiveness of KD in the management of ED.
The effectiveness of KD in children with ED: The number of participants experienced \( \geq 50\% \) reduction in seizures frequency were pooled using random effects meta-analysis after one month, three months, six months and twelve months of treatment.

One month: As depicted in Figure 1, three studies reported the effectiveness of KD after one month of treatment. The results indicated that 22.9\% benefited from the diet (21/98 children, 95\% CI 0\%-47.5\%); with statistically significant evidence of between-study heterogeneity \( I^2 = 93.1\% \), \( P < 0.001 \).

Three months: Six studies reported the effectiveness of KD after three months of treatment. Results indicated that 49.9\% benefited from the diet (269/830 children, 95\% CI 23.3\%-76.5\%); with statistically significant evidence of between-study heterogeneity \( I^2 = 98.8\% \), \( P < 0.001 \) (Figure 2).

Six months: As shown in Figure 3, four studies reported the effectiveness of KD after six months of treatment. Results indicated that 37.9\% benefited from the diet (320/872 children, 95\% CI 24.1\%-51.7\%); with statistically significant evidence of between-study heterogeneity \( I^2 = 94.45\% \), \( P < 0.001 \).

Twelve months: Three studies reported the effectiveness of KD after twelve months of treatment. The results indicated that 30.8\% benefited from the diet (237/806 children, 95\% CI 17.5\%-44.1\%); with statistically significant evidence of between-study heterogeneity \( I^2 = 94.47\% \), \( P < 0.001 \) (Figure 4).

DISCUSSION

This review aimed to assess the effectiveness of KD as a therapeutic modality for children with ED using a meta-analysis technique. This reviewing approach was designed to complement previous studies by providing an analysis of what data available; insofar it applies a rigorous statistical method to quantitatively define the efficacy of this treatment in those patients for whom there is limited number of studies.

The findings from the fourteen included studies (total of 1276 participants) suggest there is an evidence that KD is effective in the management of some cases with ED, not all cases. Reductions of seizure episodes by \( \leq 50\% \) using KD were 22.9\%, 49.9\%, 37.9\%
and 30.8% for one month, three months, six months and twelve months of treatment, respectively.

It is clearly noticed that beyond three months of treatment with KD, the number of participants experiencing $\leq 50\%$ reduction of seizure frequency is much less than those at three months of treatment. Many possible causes could have contributed to these results. One possible cause is that participants may quit using KD after three months when they start to experience side effects. Some of these side effects are life-threatening, including metabolic acidosis (8). Other reported side effects are serious infections, development of renal stones and hyperuricemia, significant gastrointestinal disturbances and allergic reactions to KD (9,10). Recent report revealed that side effects of KD were reported in about 80% (126 out of 158) of recruited children, most commonly emesis, food refusal, and hypoglycemia (11). Interestingly, researchers did not find statistically significant correlation between the severity of adverse effects and the three-month seizure reduction. Other possible causes are that some patients withdraw from these studies when noticing there is no change with the seizures frequency from the pre-KD period. Another possible cause of why beyond three months the reduction rate is much less is that the age at which the KD has started is variable in each study. Those who started KD treatment earlier in their life will showed better outcomes over time even beyond three months of treatment. On the other hand, late starting time of KD may not show obvious benefits beyond three months of treatment.

Several studies demonstrate the major mechanisms that explain the increased inhibition and/or decreased excitation induced by the KD. These involve the neurotransmitters gamma-aminobutyric acid (GABA), brain glutamate, ketone bodies (KBs) such as $\beta$-hydroxybutyrate (BHB), acetoacetate and acetone. KBs act not only as energy sources for brain cells but also contribute to reducing their glucose consumption by modulating the activities of neurotransmitters (12–14). However, there is growing evidence that KBs are more than just energy sources for brain cells, in that they can exert profound cellular, biochemical, and epigenetic changes able to attenuate brain network excitability such that occurs in epileptic patients. Recent experimental studies have appealed ketone-mediated effects on both excitatory (e.g., vesicular glutamate transporters) neurotransmission,
inhibitory (e.g., GABAergic, purinergic and ATP-sensitive potassium channels) and as well as mitochondrial targets (e.g., respiratory chain and mitochondrial permeability transition). Moreover, BHB appears to exert both epigenetic (i.e., inhibition of histone deacetylases or inhibition of histone deacetylases or HDACs) and anti-inflammatory (i.e., peripheral modulation of hydroxycarboxylic acid receptor and inhibition of the nucleotide oligomerization domain-like receptor protein 3 or NLRP3 inflammasome) activity. While the latter two effects of BHB have yet to be directly linked to ictogenesis and/or epileptogenesis, parallel evidence indicate that HDAC inhibition and a reduction in neuroinflammation alone or collectively can block seizure activity (15).

The modulation of biogenic monoamine levels was proposed as a plausible mechanism for interpreting the anticonvulsant effects of the KD. However, the specific mechanisms underlying such activities remain unclear. One study on biogenic monoamines in the cerebrospinal fluid of children treated with the KD showed that their dopamine and serotonin levels were significantly reduced from 410 to 342 and from 158 to 137 nmol/L (16.6 and 13.3% reductions, respectively) after a three-month treatment, whereas their norepinephrine levels (from 51.7 to 51.0 nmol/L, 1.4% reduction) remained unchanged (16). Those authors proposed that changes in biogenic monoamine levels are also dependent upon whether children are respondent or non-respondent to the KD.

These fourteen studies critically and systematically reviewed have dealt with the treatment of the KD in different epileptic syndromes. Different epileptic syndromes respond differently to KD. For example, patients with Doose syndrome respond significantly to KD with a reduction rate up to 100%, yet such a syndrome is so rare (17). One possible reason why one month of treatment did not show significant reduction rate is that it takes more than one month for KD to work on the brain and exert its anti-epileptic effect. These variations in epilepsy syndrome types with multiple etiologies represent an important limitation in understanding the relationships between KBs, KD, and the neuronal mechanisms in the way of seizure control. Thus, some researchers proposed variable considerations that should be taken into account upon studying these relationships: (i) chemical or physical mechanisms employed to induce seizures should follow standardized protocols; (ii) the etiologies of epilepsy are better characterized in
future clinical trials; (iii) the physiological levels of KBs should be more frequently considered in experimental treatments; (iv) the potential side effects of treatments should be systematically monitored; (v) biomarkers of treatment efficacies (levels of GABA, KBs and biogenic monoamines) should be evaluated; and (vi) novel mechanisms of action of KBs should be evaluated (18).

The study suggests multiple strength factors: it is a meta-analysis allowing a basic resource of collection of scientific evidence studies, the fourteen studies analyzed in this review were based on clinical results and showed reduction in seizures frequency used by two different types of therapeutic diets (KD and Atkins diet) in different time periods; one month, three months, six months, twelve months.

The review entails a list of limitations: it based on fourteen studies within a period of ten years, only confined to the English language, and that the age group of children varies greatly from few months and up to 17 years of age. Previous studies showed that KD is effective for short-term use; therefore, it is recommended that it should be worked on to prolong its effect in the involved patients.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Figure 1. The effectiveness of KD in children with ED after one month of treatment.
Figure 2. The effectiveness of KD in children with ED after three months of treatment.
Figure 3. The effectiveness of KD in children with ED after six months of treatment.
Figure 4. The effectiveness of KD in children with ED after twelve months of treatment.
Table 1: Systematic summary of the studies investigating the effectiveness of KD diet in children with ED included in the review

<table>
<thead>
<tr>
<th>Study number</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Research Design</th>
<th>Sample size</th>
<th>Sample Characteristics</th>
<th>Age at KD</th>
<th>Main Results</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Dominique M. Jiff</td>
<td>2016</td>
<td>Netherland</td>
<td>Experimental study</td>
<td>50</td>
<td>Age =1-18 years having Refractory seizure. Female= 42% Male= 58% KD = 28 care-as-usual = 22</td>
<td>Age of KD introduction =7.85 years Age of seizure onset=2.3 years</td>
<td>The Profile of Mood States vigor/activity = 20.86 16.50 P=0.005* The Personal Adjustment and Role Skills Scale-Third Edition productivity = 9.31 7.42 P=0.039* The Hague Restrictions in Childhood Epilepsy Scale rating severity of seizures= 6.06 7.29 P=0.038* The Social Emotional Questionnaire anxious and mood-disturbed behaviour= 8.73 15.22 P=0.049*</td>
<td>Eight patients dropped out before the study endpoint of 4 months (five patients from the KD group and three patients from the care-as-usual group).</td>
</tr>
</tbody>
</table>
### Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>Author(s)</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Study Size</th>
<th>Age</th>
<th>Gender Distribution</th>
<th>Basal Seizures</th>
<th>Seizure Freedom</th>
<th>p-value 12 weeks</th>
<th>p-value 24 weeks</th>
<th>p-value 48 weeks</th>
<th>p-value 96 weeks</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>Jeong A. Kim</td>
<td>2016</td>
<td>Korea</td>
<td>Experimental</td>
<td>104</td>
<td>Age = 1-18 years</td>
<td>Male = 55.7%</td>
<td>Female = 44.3%</td>
<td>1 to 2 Y = 35.5%</td>
<td>2 to 6 Y = 31.7%</td>
<td>6 to 18 years = 32.6%</td>
<td>Anti-epileptic drugs (mean) = 3</td>
<td>Used KD = 49%</td>
<td>Used MAD = 51%</td>
</tr>
<tr>
<td>3.</td>
<td>Tove Hallbook</td>
<td>2014</td>
<td>Scandinavia</td>
<td>Observational</td>
<td>290</td>
<td>Age = 0.5 – 18.6 years</td>
<td>Male = 50.6%</td>
<td>Female = 49.3%</td>
<td>Age ≥ 6</td>
<td></td>
<td></td>
<td>5.3 years</td>
<td>121[42](12 weeks) 98[34](24 weeks) 95[33](48 weeks) 53[18](96 weeks)</td>
<td>P-value = 0.03(12 weeks) 0.01 (24 weeks) 0.00 (48 weeks)</td>
</tr>
<tr>
<td>4.</td>
<td>Elisabeth Simon Tremblay</td>
<td>2014</td>
<td>USA</td>
<td>Experimental</td>
<td>9</td>
<td>Age = 0.5-7 years</td>
<td>Male = 88.8%</td>
<td>Female = 11.1%</td>
<td>Age at first seizure = 27.1 months</td>
<td>Anti-epileptic drugs = 3.7</td>
<td></td>
<td></td>
<td></td>
<td>Seizure freedom = 22.2%. Complete seizure control = 77.7%</td>
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</table>

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<tr>
<th>No.</th>
<th>Author(s)</th>
<th>Year</th>
<th>Country</th>
<th>Study Design</th>
<th>Age</th>
<th>Seizure Frequency Before Starting the Diets</th>
<th>Reductions After 4 Weeks</th>
<th>Reductions After 8 Weeks</th>
<th>Reductions After 12 Weeks</th>
<th>Reductions After 24 Weeks</th>
<th>Number of Cases Related to Etiologies of Seizure</th>
</tr>
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<tbody>
<tr>
<td>5.</td>
<td>Ahmed Ghazavi²²</td>
<td>2014</td>
<td>Iran</td>
<td>Experimental</td>
<td>Age=1-16 years</td>
<td>Used Atkins=50% (70% male+30% female)</td>
<td>&gt;50% reduction in Atkins</td>
<td>&gt;55% reduction in KD</td>
<td>70% reduction in Atkins</td>
<td>70% reduction in KD</td>
<td>12 cases for &lt;10 years and ≥10 years age group.</td>
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<td></td>
<td>Used KD =50%</td>
<td>(65% male+35% female)</td>
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<td></td>
<td>Seizure frequency before starting the diets: KD =15.3 Atkins=14.1</td>
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<tr>
<td>6.</td>
<td>Chenqu Suo²³</td>
<td>2012</td>
<td>China</td>
<td>Experimental</td>
<td>Age = 1.6 – 17.8 years</td>
<td>Male = 64.9% Female = 35.1% Anti-epileptic drugs ≥ 3</td>
<td>111[35](12 weeks) 83[26.2](24 weeks) 59[18.6](48 weeks)</td>
<td>70% reduction in Atkins</td>
<td>70% reduction in KD</td>
<td>12 cases for &lt;10 years and ≥10 years age group.</td>
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<thead>
<tr>
<th>No.</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Study Type</th>
<th>Number</th>
<th>Age</th>
<th>Gender</th>
<th>Anti-epileptic Drugs</th>
<th>Duration</th>
<th>Efficacy by Seizure Syndromes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.</td>
<td>Baomin Li</td>
<td>2012</td>
<td>China</td>
<td>Experimental study</td>
<td>31</td>
<td>Age = 0.58 – 7 years</td>
<td>Male = 61.2%</td>
<td>Female = 38.7%</td>
<td>≥3</td>
<td>2.5 years</td>
<td>Infantile spasms = 81.25%</td>
</tr>
<tr>
<td>8.</td>
<td>Natacha Porta</td>
<td>2009</td>
<td>France</td>
<td>Observational study</td>
<td>27</td>
<td>Female = 88%</td>
<td>Male = 12%</td>
<td>KD = 17</td>
<td>MAD = 10</td>
<td>Mean = 2.7 years</td>
<td>Seizure reduction &gt; 50%</td>
</tr>
<tr>
<td>No.</td>
<td>Author(s)</td>
<td>Year</td>
<td>Country</td>
<td>Study Type</td>
<td>Sample Size</td>
<td>Age</td>
<td>Gender</td>
<td>Anti-epileptic Drugs (mean)</td>
<td>Seizure Free (%)</td>
<td>Seizure Recurrence (%)</td>
<td>KD may have an anticonvulsive effect by decreasing the regularity of the EEG dynamics.</td>
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<tr>
<td>9.</td>
<td>Myung-Kul Yum</td>
<td>2008</td>
<td>Korea</td>
<td>Observational study</td>
<td>17</td>
<td>Age = 1-3 years Male = 76.4% Female = 23.5% Anti-epileptic drugs ≥ 2.5</td>
<td>1.7 years</td>
<td>10 [58.8] P-value=0.000</td>
<td>KD may have an anticonvulsive effect by decreasing the regularity of the EEG dynamics.</td>
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<tr>
<td>10.</td>
<td>Celina C. Martinez</td>
<td>2007</td>
<td>USA</td>
<td>Observational study</td>
<td>66</td>
<td>Age: 0.16–9.7 Y Male: 58% Female: 42%</td>
<td>3.1 years</td>
<td>Seizure free: 49% (1 w) 33% (6 m) 15% (&gt; 6 m) P value=0.31 (1 W) *Seizure recurrence: 20% (2.4 yr.)</td>
<td>Compare the recurrence rate of using KD and ADE Which was slightly lower by 20% in KD</td>
<td></td>
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<tr>
<td>11.</td>
<td>Roberto Carabello</td>
<td>2006</td>
<td>Argentina</td>
<td>Experimental study</td>
<td>11</td>
<td>Age of KD initiation=5 years 37% female 63% male Anti-epileptic drugs (mean)= 2.2 years at diet start</td>
<td>Mean=5 years</td>
<td>18.2% (seizure free) 18.2%(75% to 99% reduction) 18.2%(50% to 74% reduction)</td>
<td></td>
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<tr>
<td>12.</td>
<td>Hoon Chul Kang</td>
<td>2005</td>
<td>Korea</td>
<td>Observational study</td>
<td>199</td>
<td>Age: 0.5–17.6 years</td>
<td>Male: 55.3%</td>
<td>Female: 44.7%</td>
<td>4.8 years</td>
<td>Seizure &gt; 50% reduction: 58% (24 weeks) 41% (48 weeks) Seizure free: 33% (24 weeks) 25% (48 weeks)</td>
<td></td>
</tr>
<tr>
<td>13.</td>
<td>G. Christina Burgqvist</td>
<td>2005</td>
<td>USA</td>
<td>Experimental study</td>
<td>The FAST-KD protocol began with a fast lasting ≤ 48 h. GRAD-KD protocol began on day 2</td>
<td>Age = 1-14 years</td>
<td>Age mean = 5.3 years</td>
<td>Male = 71%</td>
<td>Female = 29%</td>
<td>Anti-epileptic drugs used prior to KD = 7.7 Anti-epileptic drugs used when KD started = 2.3</td>
<td>At 12 weeks 58% of FAST-KD had &gt; 50% reduction in seizure. Moreover, 21% seizure-free. At 12 weeks, 67% of GRAD-KD had &gt; 50% reduction in seizure. In addition, 21% seizure-free.</td>
</tr>
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</table>
with a 1:1 ratio (fat: carbohydrate + protein) by weight, full-calorie-goal meals, and then daily advanced to a 2:1, 3:1.

Seizure per week rate= 9.6 (mean)

14. Elisabeth B Marsh31 2005 USA Experimental study 67 Age=0.5-15.7 years 59.7% male 40.2% female Seizure frequency=921/month Anti-epileptic drugs =1.89

From 67 cases: 10 underwent surgery 3 underwent Vagal Nerve Stimulation implantation Remaining 41 cases: 21.9% (seizure free), 9.7% (>90% reduction), 14.6%(50%-90% reduction), 53.6% (<50% reduction)