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## Is the Ketogenic Diet Effective for Treatment in Controlling Seizures in Children with Epilepsy?

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# **Is the ketogenic diet effective for treatment in controlling seizures in children with epilepsy?**

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies  
Philadelphia College of Osteopathic Medicine  
Philadelphia, Pennsylvania

## Abstract

**Objective:** The objective of this selective EBM review is to determine whether or not the ketogenic diet is an effective treatment in controlling seizures in children with epilepsy.

**Study Design:** Review of three randomized control trials (RCTs) published in the year 2016.

**Data Sources:** Three RCTs were selected using Medline, PubMed, and Academic Search Premier. Studies were selected that reviewed the ketogenic diet (KD) in controlling seizures in children with epilepsy. All articles were chosen according to date of publication, relevance of topic, effect on quality of life, and patient-oriented evidence that matters (POEM).

**Outcomes Measured:** Seizure diaries and various scoring tests including the Hague Restrictions in Childhood Epilepsy Scale (HARCES) were utilized to assess control of seizures with number of occurrences.

**Results:** All three RCTs found that there were significant improvements in seizure control and frequency when using the KD as treatment in management of epilepsy in children. Study Ijiff et al. found seizures to be less severe after four months of using the KD as compared to care as usual ( $p=.038$ ) based on the HARCES (Ijiff DM, Postulart D, Lambrechts, DAJE, et al. *Epilepsy Behav.* 2016; 60:153-157. doi: 10.1016/j.yebeh.2016.04.033). Lambrechts et al. analyzed seizure diaries revealing a significant improvement of seizure frequency among patients on the KD in comparison to the care as usual group ( $p=0.024$ ) (Lambrechts, DAJE, Kinderen RJA, Vles JSH, Louw AJA, Aldenkamp AP, Majoie HJM. *Acta Neurol Scand.* 2017;135(2):231-239. doi: 10.1111/ane.12592). The third article, Kim et al. compared the use of KD and modified Atkin's diet (MAD), concluding that while the KD was effective in controlling seizures, there was no significant difference between the two diets ( $p=0.314$ ) (Kim DW, Kang HC, Park JC, Kim HD. *Pediatrics.* 2004;114(6):1627-1630. doi: 10.1542/peds.2004-1001).

**Conclusions:** All three studies concluded that the ketogenic diet was effective in controlling seizures in children with epilepsy. Two found statistically significant improvement in seizure control with use of the KD when compared to care as usual, but one study found no statistical significance when comparing the KD and MAD. While the KD has been found to improve seizure control and frequency, more research is indicated to investigate other possible therapeutic diets and their outcomes.

**Key Words:** Ketogenic, Diet, Epilepsy, Child, Randomized

## Introduction

Epilepsy is a chronic neurological disorder causing two or more seizures per year. Being the fourth most common neurologic disorder, about 3.4 million people suffer from epilepsy worldwide, of which, approximately 470,000 are children.<sup>1,2,3</sup> It is estimated that the median cost of hospitalization in the United States alone is about \$9,000 for a pediatric patient and treatment can range anywhere from \$522 to \$9,713 per pediatric patient.<sup>1,4</sup> These numbers are only a portion of costs as patients often suffer from other comorbid conditions requiring specialist office visits (psychologist, neurologist, occupational therapist, etc.).<sup>1</sup> Epileptic episodes also warrant hospital visits cascading into diagnostic testing, follow up appointments, and medication changes/monitoring all of which include more money tacked onto already high medical bills.

Epilepsy is a challenging disorder to manage in its own, as etiology varies from genetics, brain structure and chemistry, inborn errors of metabolism, head injuries, strokes, and idiopathic origin.<sup>2</sup> It becomes a condition where treating the underlying source is not always an easy task.

Usual treatment involves pharmacologic management. These medications are categorized according to episodic control and long-term control of seizures. Medications used to stop seizures include benzodiazepines (such as Ativan and Valium), Solofon, and Dilantin.<sup>5</sup> Other medications like Lyrica, Trileptal, Lamictal, Zarontin, and Mysoline are used in prevention.<sup>5</sup> While there are a multitude of medication classes for stopping and preventing seizures, approximately one third of epileptic patients are refractory to medication therapy.<sup>5</sup> This means medications are not adequate in their intended purposes and may even worsen or cause unwanted side effects without even providing appropriate effectiveness. Children especially are sensitive to these types of medications, bringing up the question: are there other treatment options for the management of epilepsy? This systematic review investigates the use of the ketogenic diet as an

alternative treatment in the control of seizures in children with epilepsy. The Ketogenic diet is a diet designed to be high in fats and low in protein and carbs thus creating a fasting state in the body and changing the metabolism to utilize fats.<sup>6</sup> It is thought that various restrictive diets, including the Ketogenic diet, which is discussed in this review, can help control seizures in children with epilepsy. While the exact mechanism of the Ketogenic diet in epilepsy is unclear there are associations that the change in body metabolism alters various neural responses in the brain.<sup>6</sup>

### Objective

The objective of this selective EBM review is to determine whether or not the ketogenic diet is an effective treatment in controlling seizures in children with epilepsy.

### Methods

Research was conducted and studies were limited to peer reviewed randomized control trials that analyzed the KD for management of epilepsy in children (children being anyone less than or equal to 18 years of age) chosen from PubMed, Medline and Academic Search Premiere. Articles were limited to specific keywords (ketogenic, diet, epilepsy, child, randomized) found in primary research that were published within the last ten years. Inclusion criteria were those written in the English language, populations evaluating children ages 0-18, and patient-oriented evidence that matters (POEM). Exclusion criteria included articles older than 10 years, non-primary research, and those that analyzed a population of adults older than 18 years of age.

Studies were chosen based on a variety of criteria including type of study, population, problem, and interventions involved.

The significance of interventions and treatment analyzed were determined by p values ( $p < 0.05$ ) in all three studies.<sup>7, 8, 9</sup>

Population included children 0-18 years of age with a diagnosis of epilepsy who were still experiencing seizures after trial of two or more anti-epileptic drugs (AEDs). The intervention studied was the ketogenic diet. Ijff et. al and Lambrechts compared the KD to care as usual (CAU).<sup>7, 8</sup> Care as usual is defined as the usual treatment management the child was on. Kim et. al compared the KD to another similar diet known as the modified Atkins Diet (MAD).<sup>9</sup>

#### Outcomes Measured

Outcomes were measured by both patients in the study and by the investigators conducting the study. Patients were instructed to keep seizure diaries throughout the duration of the trial.<sup>8, 9</sup> Because of the age group of the population, parents/guardians of the patients assisted in tracking of seizure diaries. Investigators were responsible for monitoring severity and frequency of seizures, as well as blood work to ensure patients were in a state of ketosis. Various scoring tests were utilized by both parties to assess improvement in control of seizures with a lower number of occurrences. Scoring scales used included the Hague Restrictions in Childhood Epilepsy Scale (HARCES).<sup>7</sup> The HARCES is a severity rating scale consisting of several questions associated with seizure intensity and frequency.<sup>7</sup>

#### Results

Ijff et al. conducted a randomized control trial on 58 patients, of which one participant withdrew prior to randomization and seven withdrew after the randomization occurred.<sup>7</sup> Of the 50 participants analyzed in the study, 8 withdrew before the trial concluded (5 from ketogenic diet group and 3 from the care as usual group).<sup>7</sup> All participants in the study were children less than 18 years of age with epilepsy who had tried two or more anti-epileptic drugs without successful control of seizures.<sup>7</sup>

Table 1: Demographics

Study	Type	# Pts.	Age (yrs.)	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Ijff (2016) <sup>7</sup>	RCT	58	At initiation: 2.1-16.5yo (7.6yo average). At seizure onset: 0-8yo (2.3yo average)	Intractable epilepsy. 1-18yo. Uncontrolled after $\geq 2$ AEDs. Not eligible for surgery.	Fatty acid oxidation disorders and related diseases. Prolonged QT syndrome. Hypercholesteremia. Severe liver, kidney, or pancreas disease. Renal tubular acidosis. Severe behavioral disorder. Malnutrition. Treatment with topiramate or acetazolamide. No positive family medical history or other RFs for kidney stones or acidosis.	8	Ketogenic Diet vs. Care as usual
Lambrechts (2016) <sup>8</sup>	RCT	58	At initiation: 2.0 - 16yo (7.6yo average). At seizure onset: 0-8yo (2.3yo average)	1-18yo w/ refractory epilepsy not eligible for surgery. Seizures uncontrolled by $\geq 2$ AEDs.	Medical contraindications or expectation that compliance with the diet was not possible due to behavioral or motivational problems.	6	Ketogenic Diet vs. Care as usual
Kim (2016) <sup>9</sup>	RCT	104	1-18yo	Children w/ drug resistant epilepsy. 1-18yo. $>4$ seizures/mo. Failure of $\geq 2$ AEDs.	History of previous dietary therapy. History of hyperlipidemia, renal calculi, or any other medical conditions incompatible with dietary therapy.	34	Ketogenic Diet vs. Modified Atkins Diet

The 50 participants in the study were randomly assigned to either the ketogenic diet (28 participants) or care as usual (22 participants) after a one-month baseline period.<sup>7</sup> Care as usual (CAU) consisted of following the patient’s normal medication regimen prior to the onset of the study.<sup>7</sup> While this study investigated other factors of the KD in epileptics including psychological and neurological components, for the purpose of this systematic review, severity/control of seizures was taken into consideration.

The study had participants complete the Hague Restrictions in Childhood Epilepsy Scale (HARCES) rating of severity of seizures to assess control of seizures during the trial.<sup>7</sup> The scoring scale uses a series of questions to determine the severity of patient’s current condition and is completed by the patient/parent/guardian. A baseline score, as well as, an endpoint score was obtained. At the end of the trial, the scoring revealed a statistically significant improvement in severity of seizures with a p value of 0.038, providing evidence that the Ketogenic diet is an effective treatment method in controlling seizures.<sup>7</sup>

Table 2. Results of Ijiff et al. based on HARCES scoring after 4 months

<b>Group</b>	<b>Baseline</b>	<b>Endpoint</b>	<b>p value</b>
<b>KD</b>	8.24	6.06	p = 0.038
<b>CAU</b>	8.32	7.29	

Kim et al. designed a randomized control trial comparing the Ketogenic diet (KD) and the modified Atkins diet (MAD) as therapeutic diets in children with epilepsy.<sup>9</sup> One hundred and four children ages 1-18 with refractory epilepsy were randomly assigned to one of the two diets.<sup>9</sup> Refractory epilepsy in this study was defined as an attempt of two or more anti-epileptic drugs

(AEDs) without successful seizure control.<sup>9</sup> 51 of the participants were instructed to follow the Ketogenic diet and 53 were to follow the modified Atkins diet. Of the 104 participants, 34 withdrew during the duration of the study.<sup>9</sup>

The diets were initiated after a four-week baseline period and assessments were made throughout the course of the study. Seizure diaries were used to monitor the frequency of seizures and an intention to treat (ITT) analysis was generated from the data (see Table 3).<sup>9</sup> While there was a reduction in seizure frequency and even remission experienced by the participants in the KD group, there was no statistically significant difference in frequency of seizures from the MAD.<sup>9</sup> All p values were >0.05. <sup>9</sup>

Data for this study is presented in Table 7, revealing a number needed to treat (NNT) of -3.<sup>9</sup> This means that for every 3 patients treated with the Ketogenic diet, one fewer could have had seizure management with the MAD.

Table 3. Results of Kim et al. percentage of baseline seizures after 3 months

<b>3 months after therapy</b>	<b>Classic KD (51) (%)</b>	<b>MAD (53) (%)</b>	<b>p value</b>
<b>Seizure free</b>	17 (33%)	13 (25%)	0.374
<b>&gt;90% reduction in seizures</b>	19 (37%)	17 (32%)	0.314
<b>&gt;50% reduction in seizures</b>	22 (43%)	22 (42%)	0.527

The RCT performed by Lambrechts et al. randomly assigned 57 patients to either the ketogenic diet or care as usual (the patient’s usual medication regimen) after a one-month baseline period.<sup>8</sup> Participants included children between the ages of 1 and 18 who had epilepsy which was not well controlled by the treatment of two or more antiepileptic drugs.<sup>8</sup> Assessments

of seizure frequency were made at baseline, six weeks, and at the endpoint of four months.<sup>8</sup> Frequency of seizures was monitored through recordings made in seizure diaries kept by the patients.<sup>8</sup>

Data from the study represented in Tables 4 and 5. Table 4 shows the mean percentage of baseline seizures in the KD group and the CAU group at the four-month endpoint of the study with a p value of 0.024.<sup>8</sup> Table 6 shows percentage of improvement in total seizures after 4 months between the two groups with a p value of 0.070. This data concludes that the KD is effective in reducing the frequency of seizures.

An intention to treat analysis was also performed in this study and the results at the endpoint assessment are represented in the Table 6.<sup>8</sup> A greater than 50% reduction of seizures was considered to be significant in the study.<sup>8</sup> 27% of patients in the KD group experienced a greater than 50% reduction compared to only 4.5% in the CAU group.<sup>8</sup> The study determined there to be a statistically significant reduction in seizure frequency of at least 50% among the KD group.

Data values from this study can also be seen in Table 7.<sup>8</sup> Similar to Kim et al. the number needed to treat (NNT) was calculated to be -3. This means that for every three patients treated with the ketogenic diet, one fewer would have had seizures managed with CAU.

Table 4. Lambrechts et al. comparison of seizures from baseline as percentage

	<b>KD (n=26)</b>	<b>CAU (n=22)</b>	<b>p value</b>
<b>Mean percentage of baseline seizures after 4 months (95% CI)</b>	56% (36-76)	99% (65-133)	0.024

Table 5. Total seizures at 4 months Lambrechts et al.

	KD	CAU	P value
Improvement	15 (65.2%)	7 (36.8%)	0.070

Table 6. Seizure frequency reduction in ITT analysis Lambrechts et al.

	KD (n) (%)	CAU (n) (%)
Responders	13 (50%)	4 (18.2%)
Seizure Free	3 (11.5%)	2 (9.2%)
>90% reduction	3 (11.5%)	1 (4.5%)
>50% reduction	7 (27%)	1 (4.5%)

Table 7. Calculated values from Kim et al. and Lambrechts et al.

Study	CER	EER	RBI	ABI	NNT
<b>Kim et. al</b>	.20	.53	1.65	-.33	-3
<b>Lambrechts et. al</b>	.182	.50	1.75	-.318	-3

## Discussion

The three randomized control trials evaluated in this systematic review showed improvement of seizure control among children with epilepsy when utilizing the Ketogenic diet as treatment.<sup>7,8,9</sup> While the studies demonstrate these findings, there are still areas of concern and question at hand.

Just as medications need to be tried and titrated, similar aspects are needed in the KD as well. Treatment is never a one size fits all but requires a trial and error type method to determine the best outcome for the patient. While the KD has been found to be a successful method of treatment of epilepsy in children, each child may require a different variation of diet. Kim et al. compared the KD and the MAD pointing out that some participants benefited more from a calorie restricted MAD rather than the regular MAD or classic KD.<sup>9</sup> The three studies were also

quick to draw attention to the side effects experienced from the KD, creating an impact on dropout rate as well. Most common side effects included gastrointestinal upset, hypercalciuria, and kidney stones.<sup>7,8,9</sup> Because of the dropout rates reported, the study population was decreased. This dropout rate could have created a stronger impact on any potential outliers and skew data. It is points like these that question what diet or variation of diet works best for pediatric patients suffering from epilepsy all while producing the least amount of side effects.

Compliance was another general theme throughout the studies regarding both following the diet and in recording/scoring. In order to maintain a state of ketosis, a specific dietary regimen is required. Because of the age of the population in the studies, parents were held accountable for not only following diet protocol, but also recording seizure diaries and answering the scoring scales used in the study.<sup>7,8,9</sup> This could have impacted results and conclusions as the patients themselves were too young to perform the intervention or record information specifically on how they were feeling.

The study conducted by Ijiff revealed a significant improvement in patients following the KD diet compared to those following CAU with a p value of .038 based on the HARCES severity rating scale.<sup>7</sup> Limitations for the study included a dropout rate of 16% and concern of compliance from the participants.<sup>7</sup> This study also explored the cognitive and behavioral impact of the KD setting up potential for future studies on other benefits of the diet.<sup>7</sup>

Lambrechts et al. noted two outliers in the study who both had an increase in frequency due to a number of small minor seizures, both of which were removed from the study.<sup>8</sup> Even without removal of the outliers, the p value was still found to be significant at 0.024.<sup>8</sup> Because the patients were experiencing a number of small minor seizures rather than usual reported seizures that were targeted for management, their data could have affected the outcome of the

small sample size hence their removal. Other limitations for their study included short duration of time and margin of error in self-recording.<sup>8</sup>

Kim et al. expressed concern of parent reliability in recording of seizure diaries when comparing the KD and the MAD.<sup>9</sup> The study determined that there was no clinical significance between the two diets with a p value of 0.314.<sup>9</sup> Both diets improved the frequency of seizures, but it was actually the MAD diet that produced less side effects.<sup>9</sup>

Interestingly enough, both Kim et al. and Lambrechts et al. concluded a significant improvement in seizure frequency, but both have a calculated NNT of -3.<sup>8,9</sup> As previously mentioned, Kim et al. compared the KD and the MAD.<sup>9</sup> The MAD being associated with less side effects possibly contributing to the NNT value and questioning the integrity of the KD over CAU.<sup>9</sup>

#### Conclusion

This paper evaluates three randomized control trials (RCTs) comparing the efficacy of the ketogenic diet (KD) in controlling seizures in children with epilepsy. Based on the three randomized control trials analyzed in this systematic review, the ketogenic diet is an effective method of treatment in the control of seizures in children with epilepsy.

However, the two calculated negative NNTs and the study proposed by Kim et al. brings to attention the need for more research on this topic.<sup>8,9</sup> Further studies should explore other therapeutic diets including more investigation on the KD versus the MAD as therapeutic diets in the management of seizures in children with epilepsy. These further findings could help benefit not only children who suffer from refractory epilepsy, but also children with epilepsy in general, by lessening the need for multiple medication use as well as reducing the financial burdens associated.

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