

RESEARCH ARTICLE

EFFICACY OF THE KETOGENIC DIET AS A THERAPY FOR INTRACTABLE EPILEPSY IN CHILDREN

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Abstract

Objective

To determine the role of ketogenic diet in the treatment of intractable epilepsy in children.

Materials & Methods

Sixty six consecutive children (1-16 years old) with intractable epilepsy whose seizure were not neurodegenerative nor febrile in origin were recruited. They received the ketogenic diet and we evaluated its effect on seizure frequency for 3 months. All these children had more than five seizures per week despite adequate therapy with at least 3-4 anticonvulsant medications. Carbohydrates were initially limited to 10 gr/day and fats constituted 75% of the total energy requirement. Response to the diet was categorized as free of seizure, 99%-75%, 50%-75%, 25%-49% and lower than 25% reduction (resistant to therapy).

Results

Fifty five patients (84%) out of 66 children initiating the diet continued it after 1 week. After 3 months, 80% of the patients kept the diet. After one week, one month and 3 months, there was a more than 50% decrease in the frequency of the seizures in 40 (60%), 50 (75%) and 39 (59%) of the patients, respectively. Three patients (4.5%) were seizure-free after 1 week, 12 (18%) were seizure-free after one month and 12 (18%) were seizure-free after three months and a significant relationship was found between seizure reduction and the type of epilepsy ($p < 0.017$).

Conclusion

The ketogenic diet should be considered as an alternative therapy for children with intractable seizures. It is more effective than many of the new anticonvulsant medications and is well tolerated by children and their families.

Keywords: Epilepsy, Ketogenic Diet, Children

Introduction

Epilepsy is a commonly treatable neurological condition with a prevalence of ten to thirty per 1000 in general population (1). Diets have been attempted extensively to control epileptic seizures throughout the centuries. The first scientific assessment using dietary manipulation was reported by Guelpa (2). Subsequently, Geyelin confirmed the fact that seizures ceased on absolute fasting. However, neither of

these studies were randomized controlled trials (3). Wilder suggested that a diet high in fat and low in carbohydrate would be similar to fasting, attributing the anticonvulsant properties to the production of ketones (4). Numerous biochemical theories have been suggested for the possible role of the diet, including the anticonvulsant effect of ketone bodies (acetoacetate beta-hydroxybutyrate), ketone reduction of alanine efflux, charge of water and electrolyte imbalance (5) or changes occurring either in the nerve cell lipid membranes or the production of neurotransmitters (6). The ketogenic diet (KD) is a high-fat, low-protein, low-carbohydrate diet used for treating medically refractory epilepsy for 86 years. The "classic" KD is based upon consumption of long-chain saturated triglycerides (LCTs) in a 3:1 or 4:1 ketogenic diet ratio of fats to carbohydrates + protein (by weight). A major proportion of the calorie (>75%) is derived from fat (7). It should be considered as the first-line therapy in glucose transporter type 1 and pyruvate dehydrogenase deficiency. It should also be considered early in the treatment of Dravet syndrome and myoclonic-astatic epilepsy (Doose syndrome) (8). This diet is rarely initiated because it is unpleasant and requires strict compliance (9). Clinical performance of KD has been different in various centers, but the diet almost always starts with fasting and then a steady increase in calories to reach a KD ratio of 3:1–4:1 (10).

This process happens in the inpatient setting after several days and it is necessary to monitor the levels of blood glucose, urine ketones, and several other metabolic variables very precisely.

Some studies suggest that the KD activates several endogenous metabolic and genetic "programs" to stabilize and/or enhance cellular metabolism, and that these fundamental changes help counter neuronal dysfunction associated with seizure activity (7, 10).

Prior to the availability of anticonvulsant medications, the ketogenic diet was used for the treatment of epilepsy. However, in the last 10 to 30 years, many researchers have evaluated the efficacy of the ketogenic diet in cases with multiple seizure types who were refractory to multiple antiepileptic drugs (AEDs) (11). Most of the studies regarding KD are retrospective and not randomized or controlled; therefore, statistical

interpretation and accurate assessment of these studies are difficult (12).

Materials & Methods

This study was a quasi-experimental survey with a sample volume of 66 children with refractory seizures who were visited at Mofid Hospital, Tehran, from October 2008 to June 2010 (32 months). Sixty six children with intractable seizures (resistant to 3-4 antiepileptic drugs) were consecutively enrolled. Patients were included in the study if 1) Age range was 1-16 years old 2) No neurodegenerative disorders and neoplasm of CNS were detected 3) The seizures were not due to febrile convulsions 4) The parents had at least primary school education. In the first meeting, our dietitian explained the ketogenic diet and the goals of the study in a comprehensible language to the family. Then, the parents signed informed consent forms and before starting the diet, parents were asked to register the frequency of their child's seizures in a diary (number of seizures/day) for a period of one week. After the children were admitted, they received the standard ketogenic diet as follows:

According to the traditional ketogenic diet, the patients were initially hospitalized in the pediatric neurology ward, their complete nutritional history with 3-day food and fluid records were reviewed by the managing dietitian. Consequently, fasting and fluid restriction was undertaken until strong urinary ketosis was achieved (3+– 4+). The patients were then fed a single daily meal of a 3:1 ratio diet (the amount derived from fat compared with the amount derived from protein and carbohydrates). The diet gradually increased in amount until the total daily required calories were provided. High-fat foods provided one third of the total daily required calories on the first day, two thirds of the required calories on the second day and full required calories on the third day of treatment. All currently administered AEDs except for acetazolamide and zonisamide were continued, and all patients remained hospitalized until acceptable tolerance was established and the education of the caregivers regarding the diet was completed (usually 1 week).

In order to evaluate treatment efficacy, the medical records of all KD patients were reviewed

retrospectively by comparing daily seizure counts of the one-week baseline before starting KD with the first week after initiation of the diet from the seizure calendars. Data regarding diet tolerability, outbreak of strong urine ketosis of higher than 3+ (50-150 mg/dL), appearance of moderate dehydration determined as more than 5% decrease in body weight compared to the baseline and the related symptoms and complications was also gathered. Finally, the results of standard laboratory tests, including blood urea nitrogen (BUN), creatinine, electrolytes, liver enzymes, cholesterol, triglyceride, and uric acid levels were recorded. Tests were considered abnormal according to the Nelson Textbook of Pediatrics, 18th edition (2008).

When the caregiver understood the protocol, patients were discharged with the prescription of supplements including carbohydrate-free multi vitamins and calcium pills based on their weight. Urinary ketones were measured once weekly for three months. The patients' families were contacted by telephone and the responder was almost always the mother.

The parents were asked to rate the effect of the diet based on the frequency and intensity of the seizures by daily documentation of speech/communication, comprehension/understanding, self-care, social interaction such as interest in others, playing, attention span/alertness, activity level, sleeping, motor skills, endurance and behavior. At the initial follow-up one month later, the children were brought to the clinic and visited by a member of the research team (a child neurologist, a pediatric resident or a managing dietitian) and the parents were asked about the frequency and intensity of the child's seizures and tolerability of the diet. Blood sugar, blood urea nitrogen (BUN), creatinine, electrolytes, liver enzymes, cholesterol, triglyceride, serum lipoproteins, AED plasma levels, and randomized urine calcium and creatinine (Ca/Cr ratio), for ruling out renal stones as one of the complications of ketogenic diet, were requested. The second follow-up visit was repeated three months after starting the diet.

Variables

The variables included sex, age, parents' education and occupation, type of seizure, presence of epileptic

syndrome, kind of epilepsy, neurological delay, EEG and neuroimaging findings (MRI, CT, SPECT), ketone after 1 and 3 months, seizure frequency after 1 week, one month and 3 months, and antiepileptic drugs (AEDs) consumption.

Data Collection

We collected our data by a questionnaire which was filled by the researcher and contained the above-mentioned variables.

Data Analysis

Data analysis was performed by SPSS-17 statistical software and differences in seizure frequency and other data were assessed using paired t-test, repeated measures and Fisher's exact test. The significance level for all tests was $P=0.05$.

Results

After 1 week of initiating the diet, 11 patients (16%) discontinued it because of its bad taste and recurrent vomiting. After 3 months, 2 cases could not keep the diet because of severe gastroenteritis and upper respiratory tract infections; therefore, 80% of the patients remained on the diet after 3 months. The mean age of the children (male: 52.7%, female: 47.3%, mean BMI: 14.9 kg/m²) was 3.6±1.9 years (1.5-11 years). The mean frequency of the seizures before intervention was 22.6 seizures/day, but diminished to 9.7 seizures/day one week after the treatment, 6.4 seizures/day after one month, and was finally reported to be 8.9 seizures/day after three months. These frequencies were significantly various throughout the study ($P < 0.05$) (Table 1).

There was a 59% reduction in mean seizure frequency after one week, 75.3% after one month, and 63.5% after three months. On the other hand, efficacy (>50% reduction in seizure frequency) was observed in 61%, 76% and 59% of the cases after 1 week, one month, and three months, respectively. Response to the diet was categorized as group 1 (becoming seizure-free), group 2 (75%-99% reduction in the number of seizures/day), group 3 (50%-75% decrease), group 4 (25%-49% decrease) and group 5 (less than 25% reduction in the number of seizures/day, meaning no improvement). Efficacy was defined as a reduction of more than fifty

percent in seizure frequency. The overall effectiveness of the diet at 1 week was as following: three patients (4.5%) in group 1, 9 patients (13.6%) in group 2, and 30 (45%) in group 3. Efficacy after 1 month was reported as 12 (18%) in group 1, 24 (36.4%) in group 2, and 14 (21.2%) in group 3. After 3 months, 18.2%, 34.8% and 6.1% were in group 1, 2 and 3, respectively (Figures 1-2).

Neither the patients' sex and age nor their parents' occupation and educational level were related to the success rate of the ketogenic diet in the three follow-up visits ($P > 0.05$). The success rate of KD was related to the type of seizure in the first follow-up ($P < 0.05$) and the highest success rate was seen in the generalized type. But neither the epileptic syndrome nor the type of epilepsy was related to success rate of the ketogenic diet in the three follow-up visits ($P > 0.05$). We found a significant relationship between the type of epilepsy and response to the diet ($P < 0.017$).

Psychomotor delay, CT scan and EEG findings had no association with the success rate of the ketogenic diet in on the first follow-ups ($P > 0.05$).

MRI and SPECT findings had no association with the success rate of ketogenic diet in none of the follow-ups ($P > 0.05$). The number of the administered drugs, Ca/Cr ratio, and also imaging findings had no association with the success rate of the ketogenic diet in the three follow-ups ($P > 0.05$). BMI had significant changes across the study which was interrelated with the success rate of ketogenic diet in all follow-ups ($P < 0.05$) (Table 2).

Discussion

The results of this analysis suggested that more than half of the children with refractory epilepsy had a clinically significant improvement after treatment with the ketogenic diet. Because these results are based on uncontrolled studies, it is possible to attribute the findings to the placebo effect, spontaneous remission, and/or random variation. However, it is unlikely that these factors account for the degree of seizure reduction seen in this trial. There is no reliable evidence from randomized controlled trials to support the use of the ketogenic diet for children with epilepsy. There are a number of larger observational studies for ketogenic diets, five of which are prospective. All authors

comment on its efficacy in a significant proportion with recognized short-term side effects, but long-term effects have not yet been addressed.

Freeman et al., from Johns Hopkins University, reported the outcome of 150 consecutive children 3, 6, and 12 months after initiating the diet (13), as well as their 3- to 6-year follow-up (14). With an intention to treat methodology, these 150 children (who had an average of 410 seizures per month and whose seizures had failed to adequately improve on a mean of 6.2 medications) had a dramatic outcome. They categorized seizure frequency reduction into four groups. Three months after the diet, they reported that 3% of the children were seizure free, 31% (46 cases) of the children had a 90-99% reduction in seizures, 26% (39 cases) had a 50-89% reduction, and 24% (36 cases) had a less than 50% reduction in their seizures. Twelve months after initiating the diet, 7% of the children were seizure-free, and another 20% had a 90% decrease in the frequency of the seizures. Three to 6 years later, 27% of the same children had few or no seizures. Most of them were now off the diet and on fewer or even no medications. In comparison, we evaluated 66 children with an average of 670 seizures per month who were taking 3-4 AEDs, and collected data one week, one month and 3 months after the diet. On the other hand, we categorized the response of the patients to diet as seizure free, 75%-99% reduction, 50-74% reduction, 25-49% reduction and lower than 25% reduction in seizures, as demonstrated in Figs. 1-2 based on the duration of the diet, respectively.

Eileen Vining (15) evaluated 51 children, aged between 1 and 8 years, that had 230 episodes of seizures per month and did not respond to 2 AEDs for 24 months. These children were followed for 12 months. Of these 51 cases, 88% continued the diet after 3 months whereas in our research, 13 cases could not continue the diet after this period of time. After 3 months, 88% of their patients remained on the diet and six cases (12%) were seizure free, 13 (25%) experienced a reduction of more than 90%, 15 (29%) had a 50-90% decrease, and 54% of the patients showed a reduction of 50% or less in seizure frequency. In our study, however, patients who did not respond (or were resistant) to 3-4 AEDs were enrolled and 80% remained on the diet. Bad taste of the diet was the main reason why they could

not keep the diet. Two of patients of Eileen Vining study, discontinued the diet because of intractable vomiting, gastroenteritis and upper respiratory tract infection (URI), and the authors did not include these two individuals in the failure group. In our study, after 3 months, reduction in seizure frequency was better (18.2% were seizure-free, 59.1% had a higher than 50% seizure reduction) than Vining's study. After 12 months, only 47% of their patients remained on the diet and 10% were seizure-free while in our study, 34% (23 cases) continued the diet and 12 cases (19%) were seizure-free for a minimum of nine months.

Similar to our study, there was no relationship between seizure reduction due to ketogenic diet and age, sex, type of seizure, EEG findings and neuroimaging. Since the 1920s, reports of efficacy have been remarkably consistent across all age groups, seizure frequencies, and international locations (16-19). In general, 10%-15% of the children who initiated the diet were seizure-free after 1 year, 30% had a 90% reduction in seizures, and 40% to 50% found that the diet was either too difficult to continue or insufficiently effective and therefore discontinued it during the first 6 months. KD is more effective compared to the wide range of anticonvulsant drugs available, even in children with refractory seizures who take newer medications. Several recent meta-analyses have evaluated literatures regarding the diet and a vast amount of prospective uncontrolled and retrospective evidence has been found despite the lack of prospective controlled studies. Dissimilarity in culture, religion and financial status has caused KD differences, such as less or no fasting, using different ratios (more rice and less fat in some Eastern countries) and increased fluid and calorie ingestion (20). Comparing the costs of KD with anticonvulsant medications shows the benefits of this diet over other treatment modalities.

According to the above-mentioned facts, a major problem we faced during the research was discontinuation of the diet in 11 patients (11/66 or 16.7%) in the first week and 13 patients after 3 months of implementing the diet; this dropout rate is almost similar to other studies using the traditional KD. Vining had a 20% dropout rate in his pediatric patients (15). In Freeman's study, 67 out of 150 children with refractory epilepsy (44.7%)

discontinued the traditional KD within 1 year of initiation (13) and 23 of the 67 families discontinued the diet before 3 months. Thirty three out of 67 patients who discontinued the diet had a feeling that the diet was ineffective and 19 found it too restrictive, 13 stopped the diet because of illness and 2 discontinued it for other reasons. Fortunately, Analysis of the causes of diet withdrawal by parents in our research showed that they mostly found it impractical and some of them complained of minor side effects in their children, like vomiting and behavioral changes (Table 3).

Side effects were also noticed in our patients during the 3-month follow-up, but longer follow-ups are required for observing potential late side effects of the KD. Investigators have classified complications as either early or late onset, depending on whether they are reported within 4 weeks of introducing the KD until stabilization, or thereafter. Acidosis, hypoglycemia, gastrointestinal distress, dehydration and lethargy are some of the unfavorable early-onset side effects of the KD which can be easily managed if the patients are not in the fasting state; however, these undesirable effects are usually temporary. Dyslipidemia, kidney stones and slowing of growth are subsequent side effects. Cholesterol and lipids adversely affect the diet. The most extensive study on dyslipidemia due to the diet followed 141 children prospectively over 2 years (20), and showed a rise in atherogenic apoB-containing lipoproteins, very low-density lipoprotein and low-density lipoprotein and a fall in the antiatherogenic high-density lipoprotein cholesterol but children who were on the KD for 6 years returned to normal lipid profile (21). In our research, there was a significant statistical relationship between KD and hyperlipidemia, both cholesterol and triglyceride, but when it occurred, adjustment of the diet ratio brought the lipid levels back to normal limits. We did not have to stop the diet because of lipid abnormalities in any children whose seizures were effectively controlled by the diet. However, triglyceride level rose to 4000mg/dl which returned to normal limits following treatment with Simvastatine. The long-term effects of these changes in lipid profile, if any, are unknown but it should be noted that most patients remain on the diet for only 2 years and then return to a diet with a normal fat amount.

A combination of acidosis, urine acidification, hypercalciuria and hypocitraturia leads to occurrence of kidney stones in 5% of the children on the KD (22). Despite the fact that anticonvulsants such as topiramate and zonisamide have carbonic anhydrase-inhibition properties and cause stone formation, using these drugs together with the diet did not increase the prevalence compared to either therapy (23). The prophylactic use of oral potassium citrate (Polycitra K) for urine alkalization significantly decreases the risk of stones (24). We followed our cases for nephrolithiasis by assessing the urine calcium/creatinine ratio with a value higher than 0.2 being considered pathologic. Pathologic values were detected in 18 (27%) of the children. Two of these children had evidence of renal stones in ultrasonography so they were referred to a child nephrologist and were treated with polycitra and more water drinking. Consequently, the renal stones disappeared and the diet continued. Children on the diet grow normally, but the growth rate of the younger children seems to be slowed down more than that of the older children (25). Those on the diet for 6 years are typically in the 10th percentile for height and weight (21). Growth seems to increase rapidly after diet discontinuation (26). Children on the KD were monitored carefully and regularly by a registered dietitian for weight and height which showed a significant reduction in weight after 3 months. Therefore, weight reduction had a statistical value after our follow-up (Table 2).

Bone density may be decreased after implementing the KD. A higher risk for skeletal fractures has been reported in children on the KD (21,27-29). Prevention with calcium supplementation, pamidronate, or lower KD ratios remains unproven.

In a recently published study focusing on tolerability and complications of the ketogenic diet, Kang and coworkers prospectively followed up a cohort of 129 children treated with the ketogenic diet for a mean duration of 1 year

Although the number of our cases was limited to reach a definite conclusion, we did not find any relationship between the rate of the decrease in seizure frequency with the age of starting ketogenic diet, epileptic syndrome, brain imaging findings, EEG abnormalities,

urinary ketone levels, and type of seizure. No such relationship has been found in other studies using the ketogenic diet (10-20), but some authors believe that certain epilepsy syndromes may be particularly well-treated by the traditional KD, including infantile spasms, Dravet syndrome, tuberous sclerosis complex and myoclonicstatic epilepsy (Doose syndrome) (30). In our research, we found a significant relationship between the type of epilepsy and the outcome of the diet (Table 3).

All our patients had 2⁺-3⁺ ketonuria after starting the diet. Because urine ketones were not checked daily during the research, ketosis could have occurred even sooner. There was no correlation between urinary ketone levels and seizure reduction, similar to a study conducted by Kossof (10).

Our study had several limitations including the dropouts, lack of assessing lipid profile, not ruling out metabolic diseases and not evaluating hypercalciuria before starting the diet, the short follow-up period (that should be extended to a minimum of 6 months) and the small number of the sample size.

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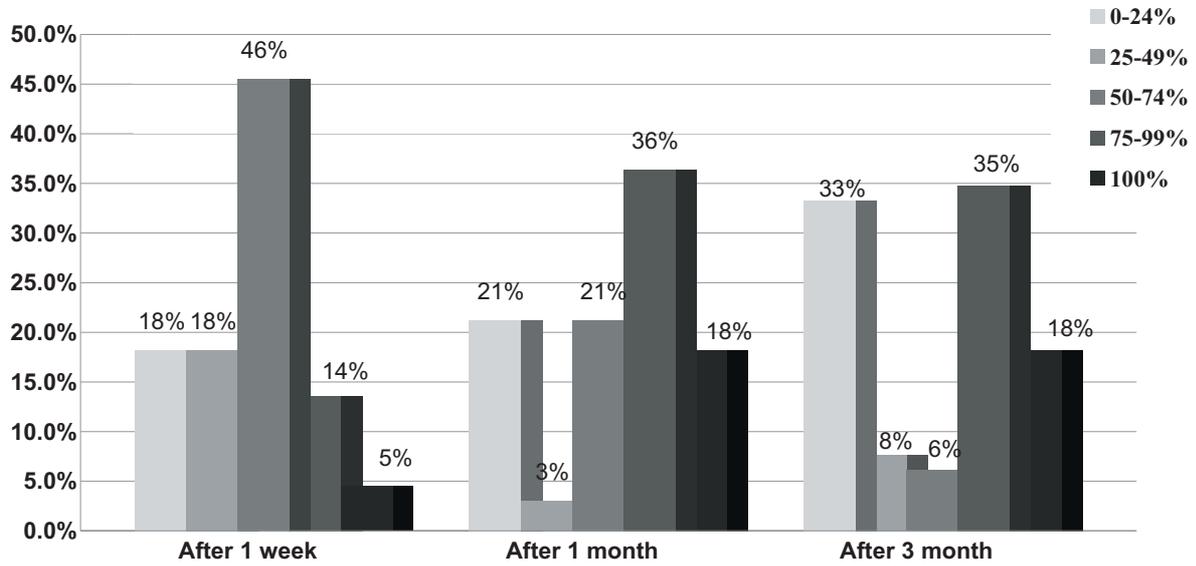


Fig 1. Percentage of decreased frequency of seizures 1 week, 1 month and 3 months after starting the diet

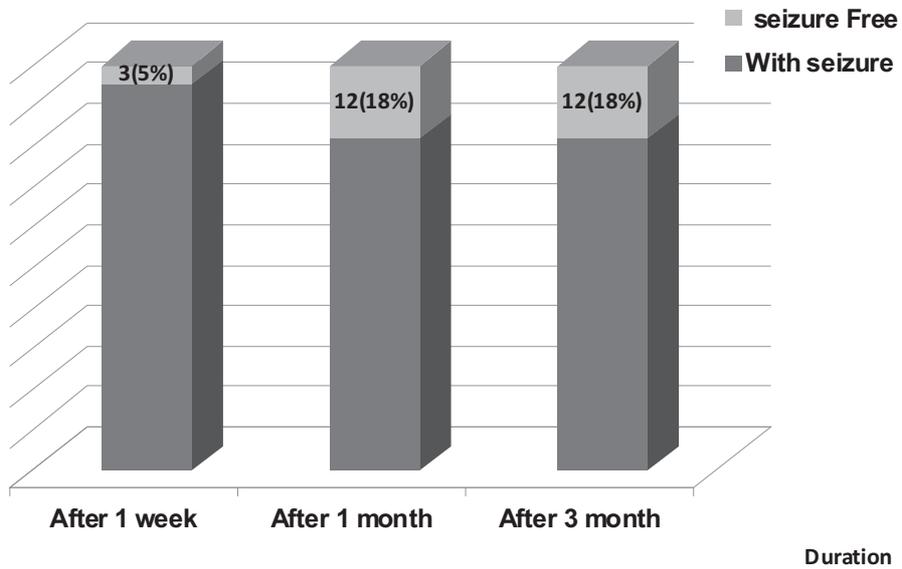


Fig.2. The number/percent of seizure-free cases and cases with seizure while on ketogenic diet after 1 week, 1 month and 3 months

Table 1. Number of daily seizures before and after the ketogenic diet

	Mean ± SD	Range	P-value
Before diet	22.6±17.5	1-70	<0.001
After 1 week	9.7±9.0	0-35	
After 1 month	6.4±9.5	0-45	
After 3 months	8.9±12.6	0-50	

Table 2. BMI before and after the ketogenic diet

BMI	Mean ± SD	Range	P-value
Before Diet	14.9±4.6	9.1-37.5	<0.001
After 1 month	14.5±4.6	8.7-37.5	
After 3 months	14.1±4.5	8.3-36.7	

Table 3. KD in the treatment of refractory seizures - study characteristics

Study/Year	Patients	KetogenicDiet	Study Design	Outcome Assessment	Compliance (%of Patients Who Discontinued KD)	Adverse Effects	Outcomes after 3 months
Freeman, Kossof	150 consecutive children treated with ketogenic diet. Age 1–16 y, 2 seizure/wk, failed at least 2 AEDs	Classic KD 4:1 fat/protein ratio	Prospective uncontrolled clinical trial	Reports by parents. Outcomes assessed at 3-, 6-, 12-month intervals	3 mo - 17% (25/150) 6 mo - 29% (44/150) 12 mo - 45% (67/150)	Kidney stones Hyperlipidemia 4%	> 50% Decrease 60% (89/150) Seizure-free 3% (4/150)
Vining 1998	51 children, 1–8y, 10 seizure/wk, failed at least 2 AEDs, enrolled from 7 sites	Classic KD 4:1 fat/protein ratio	Prospective uncontrolled clinical trial multicenter	Reports by parents. Outcomes assessed at 3-, 6-, 12-month intervals	3 mo - 12% (6/51) 6 mo - 27% (14/51) 12 mo - 45% (23/51)	Lethargy-4% (2/51) Acidosis-4% (2/51) Constipation-8% (4/51) Increased Infections-4% (2/51)	>50% Decrease 54% (28/51) Seizure-free 12% (6/51)
Present study 2008-2010	66 children, 1–16y, 5 seizure/wk, failed at least 3-4 AEDs, enrolled from Mofid Hospital	Classic KD 3:1 fat/protein ratio	Prospective uncontrolled clinical trial	Reports by parents. Outcomes assessed after 1 week, And 1 and 3 months	1week - 16% 3mo - 20%	Kidney stones Hyperlipidemia 3%	>50% Decrease 59% (39/66) Seizure-free 18% (12/66)