

The role of ketogenic diet in controlling epileptic seizures

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ABSTRACT

Objectives: To study the role of the ketogenic diet (KD) in controlling seizures in children with medically resistant epilepsy in Saudi Arabia.

Methods: This retrospective study was conducted in the Pediatric Neurology Clinic at a tertiary care epilepsy center. Thirty-one patients with medically resistant epilepsy were enrolled from 2013 to 2018. The seizure reduction variables were evaluated at 6, 12, 18 and 24 months after enrollment.

Results: Of the 31 patients, 14 (45.2%) were males and 17 (54.8%) were females. The most common types of seizures were myoclonic seizures and mixed seizures, both of which occurred in 9 (29%) of the participants. Of the participants, 15 (48.4%) had seizures one to 5 times per day. Six months after starting a KD, 2 (6.45%) of participants were seizure-free; 6 (19.35%) were seizure-free after 12 months of treatment.

Conclusion: The present study highlighted the effectiveness of KD in medically resistant epilepsy children to local population. A larger cohort is warrant to confirm these findings.

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Epilepsy is a common neurological disorder. It is characterized by seizures and affects approximately 65–70 million people worldwide.¹ Children and the elderly are most commonly affected by seizures; the condition is rarer in adults.² Epilepsy remains a challenging neurological disorder despite effective pharmacological therapies.³ More than 30% of epileptic patients do not achieve complete control of seizures with available anti-epileptic drugs (AEDs).^{1,4} Around 20-40% of patients with epilepsy have refractory

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epilepsy “failure of, adequate trials of 2 tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve the sustained seizure freedom” and who are not candidates for surgery, non-pharmacological interventions should be considered for ketogenic diet (KD) treatment.^{5,6}

The KD has been proposed for first time in 1920s as a non-pharmacologic treatment to control refractory childhood epilepsy.¹ The KD is a high-fat, low-protein, low-carbohydrate diet, with ketogenic ratio of 4:1 or 3:1 in grams which is the most commonly administered ratio.^{7,8} The KD increases the production of ketone bodies, which brain uses these ketone bodies as an energy source instead of glucose.² Some hypotheses have been proposed regarding the KD’s anti-seizure effects, suggesting that changes in the nature and degree of energy metabolism in the brain, changes in neurotransmitter function, changes in synaptic transmission, and changes in neuronal cellular properties may explain the diet’s effectiveness.⁹ Higher ketone levels correlate with better seizure control.⁹ Ten to 15% of children with epilepsy become completely seizure free on a KD.³ Furthermore, the KD has a prolonged beneficial effect even after it is discontinued.⁹

The International Ketogenic Diet Study Group strongly recommends that the KD be considered as a treatment for children with epilepsy who fail to respond to two or three anticonvulsant medications, regardless of age or gender.⁹ Our objective was to study the efficacy of the KD in children with medically resistant epilepsy in Saudi Arabia.

Methods. Participants and methods. This was a retrospective cohort study conducted in the pediatric neurology clinic at King Fahad Specialist Hospital Dammam (KFSHD). The study was ethically approved by The KFSHD Institutional Review Board (IRB) protocol (NEU032) and it was according to the ethical standards as was declared by Helsinki in 2020 review.

Study population. The study included all children aged one to 14 years who were diagnosed with medically resistant epilepsy from 2013 to 2018 and who were subsequently treated with the KD. The study data include the clinical notes from physicians and from the KD nutritionist. Exclusion criteria were as follow: utilization of the diet for reasons other than epilepsy, diets other than a classic KD, failure at diet induction, and lack of proper documentation.

Dietary protocol. The patients were first evaluated by the pediatric neurologist and KD nurse at their regular clinics. The patients’ families were provided with all the necessary KD-related education, and the relevant dietary

restrictions and lifestyle implications were discussed. A non-fasting, gradual-initiation protocol was followed. The KD was started at a 2:1 ratio (fat to protein plus carbohydrate) and then gradually increased as tolerated. The ratio of the diet was modified as necessary to maintain urine ketosis as well as to avoid acidosis, hyperketosis, and hypoglycemia. If satisfactory urine ketones were not achieved, the ratio was gradually increased up to 4:1. A ketone level measurement was performed twice daily, usually in the morning and the evening, during the period of hospital admission. The patients' blood glucose levels were measured every 6 hours using a glucometer.

The recipes were planned on the basis of the preferences of the child and their family. The menus included traditional Saudi food in order to increase their palatability and so help to ensure patient compliance. Those patients who had a nasogastric tube (NGT) or a gastrostomy tube (GT), or who were under the age of one year and had feeding problems, received a commercial KD formula (KetoCal, Nutricia Inc., Gaithersburg, MD, USA) along with different supplements, including Polycose, Fantomalt, and Bene protein. Fluids were not restricted.

Data collection and management. All the data was collected from the patient's medical records which include the following: demographic data, age at seizure onset, type of seizures, frequency of seizures, number of anti-epileptic medications used prior to KD, age at KD initiation, and changes in seizure frequency on a KD. The terminology of seizures was defined based on the International League Against Epilepsy's (ILAE).¹⁰

In this study the seizure frequency data was collected at baseline and 6, 12, 18, and 24 months after participants started the KD, or at any point within this time frame if the diet was discontinued before 6 months of adherence.

Statistical analysis. The data was collected and analyzed by using IBM statistical package for the social sciences version for Windows, version 21 (IBM Corp., Armonk, N.Y., USA). All categorical variables were presented in frequency and percentages while mean and standard deviation was calculated for age at seizure onset and age at initiation of KD.

Results. Demographics. Thirty-one patients met the inclusion criteria and began KD. There was not significant difference between male 14 (45.2%) and female 17 (54.8%) ($p=0.59$). The mean age at the initiation of the KD was 7.2 ± 3.6 ; participants ranged in age from one to 14 years, with no significant difference among the patients age group ($p=0.832$). There was

significant difference in the distribution of patients based on seizure onset ($p=0.001$) with the range of age at seizure onset was zero to 24 months (Table 1).

Type of seizure. Participants suffered from myoclonic seizures ($n=9$), tonic seizures ($n=3$), generalized tonic clonic ($n=5$), epileptic spasms ($n=2$), mixed seizures ($n=9$) and infantile spasms ($n=3$). The most common types of seizures in the sample were myoclonic (29%) and mixed seizures (29%) (Table 2).

Efficacy. Patients with higher baseline seizure frequency reported a more favorable response to the KD 12-months after starting a KD ($p=0.000$) (Table 3). Two (6.45%) patients were seizure free 6 months after starting a KD, although this value was not statically significant ($p=0.611$); 6 (19.35%) patients were seizure free 12 months after starting a KD, which is statistically significant ($p=0.000$) (Table 3).

Table 1 - Demographics and clinical characteristics of patients.

Variables	n (%)	P-value
<i>Gender</i>		
Male	14 (45)	$p=0.590$
Female	17 (55)	
<i>Distribution of patients based on age</i>		
1-4 Years	9 (29)	$p=0.832$
4-7 Years	9 (29)	
7-10 Years	6 (19.4)	
10-14 Years	7 (22.6)	
<i>Distribution of patients based on seizure onset</i>		
0 -1 Month	7 (22.6)	$p=0.001$
1 - 6 Months	15 (48.4)	
6 -12 Months	5 (16.1)	
12 -18 Months	2 (6.5)	
18 -24 Months	2 (6.5)	
<i>Seizure frequency at baseline</i>		
>5/Day	13 (42)	$p=0.096$
1-5/Day	15 (48)	
Others	3 (10)	

Table 2 - Distribution of patients based on seizure type.

Seizure type	n (%)
Myoclonic	9 (29)
Tonic	3 (9.7)
Generalized tonic clonic	5 (16.1)
Epileptic Spasms	2 (6.5)
Mixed Seizures	9 (29)
Infantile Spasms	3 (9.7)
Total	31 (100)

Table 3 - Seizure frequency at baseline and after Ketogenic diet.

Seizure frequency	Baseline	After initiating ketogenic diet			
		6 Months	12 Months	18 Months	24 Months
Seizure free	0	2	6	4	2
>5/Day	13	2	0	0	0
1-5/Day	15	14	5	3	0
Others	3	7	5	0	0
NA	-	6	15	24	29
Total	31	31	31	31	31
		<i>p</i> =0.611	<i>p</i> =0.072	<i>p</i> =0.000	<i>p</i> =0.000
		NA - Not available			

At the 12-month follow up, 6 patients (19.35%) were seizure free, 5 patients (16.12%) continued to show >50% seizure reduction and 3 patients showed this outcome at 18-month interval (Table 3).

Discussion. Our aim was to evaluate the effectiveness of the KD as one treatment option for children with drug resistant epilepsy.

Patients with very frequent seizures showed more improvement 12 months after starting a KD than those with fewer than five seizures per day; this is consistent with previous studies.⁹ The ratio of male (45.2%) to female (54.8%) participants in our study is comparable to that of other studies (some of which are 46% male and 54% female).⁹ The mean age at which the participants in our study began a KD was 7.2±3.6 also similar to other studies, which have included participants with a mean age of 7.9 years,¹¹ 7.5 years,¹² and 7.8 years.⁶

In our study, 2 patients (6.45%) were seizure free 6 months after starting a KD; 6 (19.35%) were seizure free 12 months after starting a KD. Lee et al documented seizure-free rates of 14%, 16%, 17%, and 14% 3, 6, 12, and 24 months after starting a KD, respectively.¹⁴ Six months after starting the KD, their reported seizure-free rate was higher than our rate of 6.45%; this is probably due to Lee et al.'s¹⁴ larger sample size.¹⁴ At 12 months, however, our participants reported a higher seizure-free rate of 19.35%.

In 2014, a prospective study was conducted with 61 patients with Lennox–Gastaut syndrome (LGS) and refractory epilepsy.¹² In that study, 15% (3 of 20) participants were seizure free 18 months after starting a KD; 2 of those remained seizure free several years after discontinuing the diet.¹² A KD seems to be most effective in controlling tonic, atonic, and myoclonic-atonic seizures.¹² Studies have highlighted the possible benefits of dietary interventions, which should be

considered as an initial treatment for children with refractory epilepsy before more invasive interventions are used.¹ In our sample, myoclonic and mixed seizures were the most common types 29% for each. However, the KD has demonstrated high effectiveness in treating patients with generalized seizures.⁹ Several studies have demonstrated the continuing effectiveness of the KD diet even after it is discontinued.¹²

We followed a non-fasting, gradual-initiation protocol for the low incidence of potential adverse event in our group.^{3,4} The use of a KD is contraindicated for certain metabolic disorders, for example, carnitine deficiency, fatty acid oxidation defects, and pyruvate carboxylase deficiency, and care should be taken to rule out such metabolic disorders prior to initiating the diet.¹²

Therefore, we suggest caution when initiating a KD in infants and young children aged less than three years old as well as in children with a lower weight, especially when the diet is initiated on an outpatient basis. There are 4 treatment options available for DRE, namely medication, KD, neurostimulation devices (e.g., vagus nerve stimulation and responsive neurostimulation), and epilepsy surgery. In developing countries, where around 80% of patients with epilepsy live, some treatment options, including newer AED, may not be available, while expensive treatment options may not be affordable. Cost-effective, sustainable epilepsy care options are thus needed to decrease the treatment gap between developed and developing countries.

Limitations. This study has some limitations. It did not use a double-blind design. Furthermore, the small sample size may limit the statistical value of the findings. Seizure outcomes were measured based on caregiver reports and subjective errors could be included in the data.

In conclusion, The current study demonstrates

the effectiveness of a KD as a non-pharmacological treatment for reducing the frequency of seizures in children with medically resistant epilepsy. Patients with higher baseline seizure frequency reported a more favorable response to the KD. Our findings add to the growing body of literature on this topic and especially to the body of studies on this topic conducted in Saudi Arabia.

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