Original Article

Effect of a ketogenic diet on decrease of seizures in refractory epilepsy among children (infancy to 14 years old) in Saudi Arabia: a cross-sectional study

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Background: Refractory (intractable/pharmaco-resistant) epilepsy in children is considered if disabling seizures continue despite appropriate trials of two anti-seizure drugs, either alone or in combination. Ketogenic diets are used as a treatment option in many countries for children with refractory seizures; however, few patients have tried it in Saudi Arabia. Therefore, we examined the relationship between the exposure to a ketogenic diet and its effect in decreasing seizure frequency in infants and children up to 14 years who had refractory epilepsy and assessed factors that could improve the outcome of seizures.

Methods: This cross-sectional study was conducted at King Fahad Medical City, Riyadh, Saudi Arabia. Data were collected by reviewing medical records of eligible children (infants and children up to 14 years old) with refractory epilepsy who were on ketogenic diets. Socioeconomic data of the parents (guardians) were collected via phone interviews after verbal consent from the parents (guardians).

Results: We recruited 95 children (aged 10 months to 14 years) with refractory epilepsy and on Ketogenic diets. Up to 44% of patients on 3:1 and 4.5:1 ratio ketogenic diets had decreased seizure frequency while patients on 1:1 and 2:1 ratio ketogenic diets showed no decrease in seizures. Patients with generalized epilepsy who were on ketogenic diets had the most improvement in seizure outcomes (56.1%) and patients on ketogenic diets who were ambulatory indoors and outdoors (66.7%) showed a high level of improvement in seizure outcomes compared to patients with who were non-ambulatory (21.9%). Lower improvements in seizure frequency in epileptic patients on ketogenic diets were associated with low education levels of parents (33.3% high school *vs.* 50% undergraduate school), low incomes [<11,400±7,560.864 Saudi riyal (SR)], and diagnosis of seizures in patients >8 years old.

Conclusions: Ketogenic diets are a promising approach for treatment of refractory epilepsy among children. The improvement in seizure outcomes was associated with higher ratios of ketogenic diets (3:1 and 4.5:1), and higher physical activity. Sociodemographic factors, including parents' (guardians') education levels and income influenced the improvement of seizures.

Keywords: Ketogenic diet; refractory epilepsy; seizure; children; Saudi Arabia

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Introduction

Background

Epilepsy in pediatric and adolescent patients is considered to be a disease of the brain defined by the International Bureau for Epilepsy (IBE) and the International League Against Epilepsy (ILAE) as any of the following conditions: (I) at least two unprovoked seizures happening more than 24 hours apart; (II) one unprovoked seizure and a likelihood of further seizures above the average recurrence risk (at least 60%) after two unprovoked seizures occurring over the course of the following ten years; (III) a finding that an epilepsy syndrome exists (1,2). These seizures are defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (2). Alternatively, refractory (intractable/pharmaco-resistant) epilepsy in children is considered if disabling seizures continue despite appropriate trials of two anti-seizure drugs, either alone or in combination (2). In their lifetime, up to 65% of individuals suffering from epilepsy may experience seizures that could be controlled through the use of antiepileptic drugs (ASMs) or go into spontaneous remission (3). Nonetheless, this results in a significant proportion of patients who are unresponsive to drug therapy (refractory seizures) (3,4). The current treatment options for refractory epilepsy include epilepsy surgery, vagus nerve stimulation, and a ketogenic diet (KD) (3).

Dietary therapy, specifically a KD, is a crucial approach for treating refractory epilepsy. The KD may have both immediate and long-term effects. KD, characterized by high fat, low carbohydrate, and moderate protein content, mimics the body's starvation state, shifting energy production from glycolysis to ketone bodies (3). Emerging experimental studies demonstrate that ketones cause gene up-regulation, which increases the number of mitochondria in neurons and glial cells decreasing the risk of seizure (3-5). The classic KD involves a strict 3:1–4:1 ratio of fats to combined carbohydrates and proteins, with several variations developed in an attempt to improve tolerance and decrease adverse effects, including weight loss, gastrointestinal (GI) symptoms, and low mood (6).

The modified Atkins diet (MAD) is a less restrictive variation of the KD, which is initiated for outpatients without fasting; it allows unlimited protein and fat intake and does not restrict calories or fluids (7). The MAD alternative dietary therapy has been prescribed for pediatric patients unable to tolerate the restrictions and adverse effects of KD. A MAD could be the primary choice for the treatment of intractable epilepsy in children, although the classic KD with its higher fat ratio is more suitable as the first line of diet therapy in patients aged <2 years, for rapid implementation of dietary therapy as these young children have been found to be more susceptible to epileptic encephalopathy as a result of prolonged intractable seizures (8).

Rationale and knowledge gap

A review of the literature shows that the decrease in seizure frequency of patients with epilepsy on the ketogenic diets was high; overall, 45.8% of children treated with the KD had >50% response to the ketogenic diet. In randomized controlled trials, children on KD were found to be up to three times more likely to have no seizures, and up to

Highlight box

Key findings

- Up to 44% of patients on 3:1 and 4.5:1 ratio ketogenic diet (KD) had decreased seizure frequency in children with refractory epilepsy among children.

What is known and what is new?

- The evidence regarding KD effects on refractory epilepsy in Saudi Arabia is currently inadequate.
- Compared to previous studies, we had larger participant numbers and found that KD positively affects the improvement rate of refractory epilepsy among Saudi patients. The rate of improvement among patients on ketogenic diets was statistically significant [44.2% (95% CI: 34.5–54.2%), P=0.008]; and the improvement rate influenced by various social determinants and lifestyle factors.

What is the implication, and what should change now?

- Limited hospitals in Saudi Arabia offer KD therapy for refractory epilepsy, but it may improve treatment and prognosis for children with epilepsy and should be more widely available as an alternative treatment or adjunct to surgical resection.
- KD is less invasive, and perhaps more economical which means less hospitalization improving the patient's quality of life.

six times more likely to have decreased seizure frequency by ≥50% compared to children on anti-seizure medications alone. Although surgical treatment is the gold standard for resectable epileptic lesions, a decrease in the frequency of seizures was higher among children who underwent surgery and followed a KD (9).

The reduction of seizures among children is similar to adults treated with KD; they were up to five times more likely to have ≥50% reduction in seizure frequency (10). Traditionally, the KD is the gold standard for the treatment of metabolic diseases such as the glucose transporter protein 1 deficiency syndrome and pyruvate dehydrogenase deficiency with more than 70% patients showing ≥50% decrease in seizures. The KD is an important treatment alternative for patients with refractory epilepsy who are ineligible for surgery (11). Modified KD therapies are effective in decreasing seizure frequency, severity, and improving quality of life, and could offer the best chance of improvement for patients whose seizures have persisted despite surgical intervention and vagal nerve stimulation therapy (12). A recent meta-analysis showed that 53% of adults with intractable epilepsy can achieve >50% reduction in seizure frequency with a KD, indicating that it is a promising treatment for refractory epilepsy (13).

To date, many researchers have investigated the effect of KD in children with epilepsy (11-14). However, in Saudi Arabia, there is scarce evidence of the effect of KD on seizure frequency. A review of eight children (infancy–14 years) from a specialized research center in western Saudi Arabia (2) was too small a sample size to extrapolate the results to the entire Saudi population. Another study in eastern Saudi Arabia compared the effect of antiepileptic medications and KD on seizure outcomes (15). It showed KD were effective in treating medically resistant epilepsy; however, these findings could be underestimated due to recall bias as the seizure outcomes were based on caregivers' reports and could include subjective errors in data collection. A study at the Pediatric Neurology Clinic at a tertiary care epilepsy center in the eastern region investigated the efficacy of KD in 31 children (1–14 years) with medically resistant epilepsy (15).

Objective

Our study was designed to assess the effect of KD on decrease of seizure frequency in children with refractory epilepsy and to investigate its effect on epilepsy control, depending on various social determinants, including age, gender, socioeconomic status, and clinical risk factors. This article is presented in accordance with the STROBE reporting checklist (available at https://tp.amegroups.com/article/view/10.21037/tp-23-211/rc).

Methods

Study population and design

We conducted an analytical cross-sectional study that targeted infants and children up to 14 years old, who have refractory epilepsy and attend King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. All files for epilepsy patients who currently were or previously had been on a ketogenic diet (2008 to 2021) were reviewed between September 2021 and December 2021, using the simple random sampling technique.

Method of sampling and study setting

We studied the effect of KD on infants and children with refractory epilepsy in Saudi Arabia, as there is insufficient national research regarding this topic. We selected KFMC because it is one of the few tertiary hospitals in Saudi Arabia with a specialized epilepsy center that offers KD treatment as a treatment option for refractory epilepsy and all cases of epilepsy requiring KD management are referred here.

The eligibility criteria were infants and children up to 14 years with refractory epilepsy, who were on KD, and followed up at KFMC. The pediatric epileptologist and ketogenic diet nutritionist provided a list of eligible participants. Patient data were collected by reviewing the medical records and hospital database of the eligible participants, and collected in a data collection sheet then transferred into Excel sheets before statistical analysis.

The exclusion criteria were adults, neonates, and children above 14 years, patients diagnosed with epilepsy who responded 100% to anti-seizure medications, other diseases that used a KD treatment (including obesity, BMI >30), and children with history of having surgical intervention to treat epilepsy. Information missing from the medical records (such as parents'/guardians' socioeconomic status) was collected by conducting phone interviews after obtaining verbal consent from the patients' parents (or guardians) (phone consent attached to Appendix 1). The duration of the phone interviews was approximately two minutes, and the purpose and risk of participation was explained to the participants' parents (or guardians).

Study measures

The main exposure in this study was the KD for up to 12 months. Details about the KD protocol used by physicians and nutritionists at KFMC was given in details (Ketogenic diet protocol pathways in Appendix 2). KD was initiated in the inpatient setting according to a protocol-based on the John Hopkins over 3–4 days. In summary, it is based on the ratio of fat to protein and carbohydrate in a meal. For example, if a meal has 64 g of fat, 12 g of protein and 4 g of carbohydrates; 64 g fat:16 g protein and carbohydrates (12 g proteins + 4 g carbohydrates); this is a 4:1 ratio. The classic KD uses long chain triglycerides in a 4:1 ratio (fat to non-fat) and sometimes a ratio of 3:1 is sufficient to produce ketosis; urine ketones, the patient's weight and side effects (such as GI symptoms, hypoglycemia, dehydration, diarrhea etc.) were assessed to monitor the patients' progression. Berceuse ketosis may not be achieved in the inpatient setting as it may take weeks to months to occur, close monitoring continued with the KD dietician together with the parents. The diet was given a period of three months to determine its ability to produce adequate ketone and/or its effectiveness in decreasing seizures.

A table of recommended daily allowances is used to calculate calorie and protein requirements (Ketogenic diet protocol pathways is attached in Appendix 2). Usually, the initiation of KD ratio is 1:1. The gradual increase in ratio of fat to carbohydrates and protein sequentially to 2:1 then 3:1 and ultimately 4:1 is dependent on the patient's response (ketosis), absence of hypoglycemia, tolerance and side effects if any. If adequate Ketosis (large on urine ketone stick) is achieved at 3:1 we do not advance further to 4:1.

However, the recommended starting ratio is based on age. Although this protocol was developed based on an international guideline, it was personalized to the Saudi population because sociodemographic, and genetic cultural background varies between populations. This approach of personalized management has been previously used (16); additionally, the degree of ketosis may vary among individuals. Two different individuals within the same age group and weight may experience a completely different level of ketosis on the same KD ratio. This difference is due to individual's variations in energy metabolism and expenditure (16). Therefore, a 2:1 ratio (low glycemic index) is used for 12-year-old patients, a 3:1 ratio is better for patients aged <18 months, and 4:1 and 3:1 ratios are used for patients aged 19 months to 14 years. In case of obesity, a high fat content is needed to compensate the high level of fat associated with obesity; therefore, a ratio of 3:1 is usually used; as higher ratios result in greater degrees of ketosis (17).

The primary outcome is an improvement in refractory epilepsy of infants and children up to 14 years old. Based on previous studies, a positive outcome was defined as ≥50% decrease in the frequency of seizures during the previous 12 months. Patients were categorized into two groups, those who improved (≥50% decrease in the frequency of seizures during the previous 12 months) and those who did not improve (<50% decrease in the frequency of seizures during the previous 12 months) (18).

The children's sociodemographic data were collected, including age (measured in months for infants and years for older children), sex (male and female), nationality (Saudi and non-Saudi), and education level of parents (or guardians). Parents' (or guardians') sociodemographic data was collected, including age in years, marital status, income, educational level, occupation, living area, health insurance, and access to a government or private hospital. Other factors, which could influence the exposure to KD and the outcome (i.e., confounders) were assessed, including treatment history, presence of risk factors associated with not following the KD, prescribed medication/drugs for patients on KD, ability to afford KD and related products, ability to continue the KD treatment, relapse, adverse effects and complications, duration of the treatment, and ketonuria. Data about syndromes such as Infantile epileptic encephalopathy, Angelman syndrome, Lennox–Gastaut syndrome (LGS), MMFSI, Dravet syndrome etc. was obtained. Detailed information about the seizures was obtained, including the duration, type and location, and seizure semiology, which is a tool that allows localization of the symptomatogenic zone that either overlaps or is in close proximity to the epileptogenic zone. This is of particular importance in cases of magnetic resonance imaging-negative focal epilepsy (7) to identify the type of seizure more responsive to KD.

Power sample size and statistical analysis

The sample size was calculated using Z=1.96 for 95% confidence interval (CI) P=0.50, d=0.05 and the sample size was n=208. Our study population was patients (infants to 14 year olds) with refractory epilepsy in KFMC, Riyadh, who attended outpatient clinics between 2008 and 2021. For this study, a sample size of 208 was needed based on a 50% prevalence of decreased seizures among children (10), an 85% confidence interval, and a 5% margin of error,

Table 1 Seizure outcomes and relapse of children with refractory epilepsy (N=95)

Seizure outcomes	Ketogenic diet		P value
	N	% (95% CI)	
Not improved	53	55.8% (45.8–65.5%)	0.008
Improved	42	44.2% (34.5–54.2%)	

P value is statistically significant at <0.05.

using the single proportion formula:

$$n = Z2\alpha P(1-P)/d2 \quad [1]$$

As the data were collected from existing medical records, some patient data (mainly sociodemographic) were unavailable and collected by making individual telephone calls to parents (or guardians); their response rates were very low and information was incomplete. Given these difficulties, the original sample size was recalculated based on the prevalence of children who improved with KD (i.e., 45%) and the sample size changed to n=95.

The Statistical Package for Social Sciences (IBM SPSS Statistics), version 26 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Categorical variables (including gender, categories of body-weight percentiles) were expressed as frequencies and percentages. Continuous numerical variables (age, income) did not follow the normal distribution and were expressed as means and standard deviations. Univariate binomial logistic regression analysis was conducted to assess the factors that significantly contributed to the improvement of seizures. Common confounders (type and duration of KD treatment, age at the time of the study, gender, weight, class of seizures, and presence of other medical conditions) were entered into a multivariate regression model to adjust for their effects on the observed reduction in seizure frequency. Statistical significance was considered at P values <0.05.

Ethical statement

This study was conducted according to the guidelines of the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of King Saud University College of Medicine (No. E-21-6123-CMED-305/F4) in agreement with the Institutional Review Board of the KFMC (No. 21-347E), after signing a material transfer agreement (MAT) by the provider at KFMC. Data collected from hospital records but verbal informed consent from the patients' parents (or guardians) was obtained to complete the missing information from the medical records such as parents'/guardians' socioeconomic status (phone consent attached to Appendix 1).

Results

We recruited 95 children (aged 10 months to 14 years) with refractory epilepsy and on KD. The rate of improvement among patients on KD was statistically significant [44.2% of patients (95% CI: 34.5–54.2%), P=0.008] (*Table 1*).

Table 2 shows the demographic characteristics of participating children divided into two groups (improved patients and unimproved patients). There were no differences in the mean age of the parents or children who improved on the KD compared with those who did not improve on the KD. However, other sociodemographic factors varied between the children in the KD group. The parents of children who showed improvement had higher incomes than the parents whose children had no improvement [Saudi riyal (SR) 15,333±7,252, and SR 11,400±7,561, respectively]. The female patients showed slightly more improvement than the male patients (49.0% *vs.* 39.1%) did. Most of the epileptic patients who lived outside Riyadh showed a slightly higher rate of improvement compared to those living in Riyadh (46.2% *vs.* 35.3%). About 80% and 100% of patients whose parents were divorced or widowed showed less improvement, respectively. Children whose parents had high school or lower education levels did not show as much improvement as the children whose parents had an undergraduate degree or a higher qualification.

The patients with generalized epileptic seizures (56.1%) had the most reduction in seizure frequency compared to those with focal and spasm epilepsy (42.9% and 50.0%, respectively). The seizures semiology (localization of the symptomatogenic zone) showed no improvement for patients with migration epilepsy and epilepsia partialis continua; however, there was a marked decrease in seizure frequency for patients with tonic spasms, focal, multiple, and concurrent seizures (80%, 50%, and 50%, respectively) (*Table 2*). Moreover, patients diagnosed with syndromes such as Infantile epileptic encephalopathy, Angelman syndrome, Lennox–Gastaut syndrome (LGS), MMFSI, Dravet syndrome etc. showed no statistically significant associations with improvement of seizures (data was not shown).

Patients who were ambulatory indoors and outdoors (66.7%) and wheelchair-bound patients (53.8%) had

Table 2 Distribution of sociodemographic and clinical characteristics of study participants N=95 (not improved and improved patients)

Characteristics	Seizure outcomes	
	Not improved	Improved
Age of children (year)	11.2±4.6	12.4±5.1
Mother's age (year)	38.72±7.266	38.61±6.436
Father's age (year)	43.83±7.682	44.11±8.574
Sex of children		
Male	28 (60.9)	18 (39.1)
Female	25 (51.0)	24 (49.0)
Monthly income, SR	11,400±7,560.864	15,333.33±7,251.775
Location		
Riyadh	11 (64.7)	6 (35.3)
Outside Riyadh	42 (53.8)	36 (46.2)
Marital status of parents[†]		
Married	20 (55.5)	16 (44.4)
Divorced	4 (80.0)	1 (20.0)
Widowed	1 (100.0)	0 (0.0)
Mother's education		
Primary school	3 (75.0)	1 (25.0)
Intermediate	1 (100.0)	0 (0.0)
High school	6 (75.0)	2 (25.0)
Undergraduate degree	15 (75.7)	11 (42.3)
Postgraduate degree	0 (0.0)	2 (100.0)
Diploma	0 (0.0)	2 (100.0)
Father's education[†]		
Primary school	2 (100.0)	0 (0.0)
Intermediate	1 (100.0)	0 (0.0)
High school	8 (66.7)	4 (33.3)
Undergraduate degree	12 (50.0)	12 (50.0)
Postgraduate degree	0 (0.0)	2 (100.0)
Diploma	1 (100.0)	0 (0.0)
Private health insurance[#]		
Yes	5 (71.4)	2 (28.6)
No	11 (47.8)	12 (52.2)
Working mother[#]		
No	13 (54.2)	11 (45.8)
Yes	3 (50.0)	3 (50.0)
Father's occupation[*]		
Unemployed	2 (50.0)	2 (50.0)
Worker	1 (50.0)	1 (50.0)
Employee	3 (100.0)	0 (0.0)
Military	1 (20.0)	4 (80.0)
Professional	3 (42.9)	4 (57.1)
Etiology of epilepsy		
Infection	2 (40.0)	3 (60.0)
Genetics	20 (48.8)	21 (51.2)
Prenatal event	6 (85.7)	1 (14.3)
Metabolic disorder	0 (0.0)	4 (100.0)
Autoimmune disorder	2 (100.0)	0 (0.0)
Structural	2 (40.0)	3 (60.0)
Unknown	28 (90.3)	3 (9.7)
Classification of seizures		
Generalized	36 (43.9)	46 (56.1)
Focal	4 (57.1)	3 (42.9)
Spasm	3 (50.0)	3 (50.0)
Seizure semiology		
Myoclonic seizures	3 (60.0)	2 (40.0)
Tonic-clonic seizure	18 (56.3)	14 (43.8)
Multiple seizures	10 (58.8)	7 (41.2)
Tonic spasm	1 (20.0)	4 (80.0)
Migration epilepsy	1 (100.0)	0 (0.0)
Focal	3 (50.0)	3 (50.0)
Spasm	14 (60.9)	9 (39.1)
Multiple and concurrent seizures	2 (50.0)	2 (50.0)
Epilepsia partialis continua	1 (100.0)	0 (0.0)
Family history of epilepsy[†]		
Yes	3 (50.0)	3 (50.0)
No	21 (58.3)	15 (41.7)
Physical activity level of patients		
Spastic cerebral palsy	25 (78.1)	7 (21.9)
Wheelchair-bound	6 (46.2)	7 (53.8)
Hypotonia	8 (57.1)	6 (42.9)
Ambulatory indoors and outdoors	8 (33.3)	16 (66.7)
Ambulatory indoors	6 (50.0)	6 (50.0)
Medical history other than epilepsy		
Yes	6 (60.0)	4 (40.0)
No	44 (51.8)	41 (48.2)

Data are presented as n (%) or mean ± SD. [†], data was available for N=42; [#], data was available for N= 30; [*], data was available for N=21. SR, Saudi riyal; SD, standard deviation.

decreased seizure frequency compared to the patients with spastic cerebral palsy (CP) (21.9%). There was no statistically significant difference in the seizure improvement of patients with and without a family history of epilepsy.

Table 3 summarizes the seizure distribution and diet history of the patients. At the start of the ketogenic diet, most patients were at the 50th percentile for weight. The improvement was greater among patients (57%) who were at the >50th weight percentile. Almost all patients who improved on the KD had >50% reduction in the frequency of seizures, one patient had 90% reduction in seizures and four patients were seizure free. Fifteen out of 53 patients who did not improve on the KD had <50% reduction in the frequency of seizures, one patient showed temporal improvement, and two patients were worse with the diet.

In our study, the children had been diagnosed with seizures at different ages. Children who were diagnosed aged ≤1 year showed an improvement of >50% compared to those who were diagnosed at 8 years and showed less decrease in seizures.

Patients who were on a 1:1 KD and 2:1 KD showed no improvement although 44% of patients on 3:1 diets and 4.5:1 diets showed a decrease in seizure frequency. Patients (71.4%) who changed their diet ratios had decreased seizure frequencies and 41% of them are still on the KD. In the 3:1 diet group, 13.9% of the patients had GI symptoms, including nausea, vomiting, and diarrhea. However, the prevalence of adverse effects was comparable in patients who improved on KD compared with those not improved (47% *vs.* 52%, respectively). Forty percent of patients

Table 3 Distribution of seizures and diet history for children on ketogenic diets (N=95)

Variables	Seizure outcomes	
	Not improved	Improved
Age of seizure onset*		
1–3 months	14 (66.7)	7 (33.3)
3–6 months	26 (52.0)	24 (48.0)
6–12 months	9 (56.3)	7 (43.8)
1 year	2 (50.0)	2 (50.0)
2 years	1 (100.0)	0 (0.0)
5 years	0 (0.0)	1 (100.0)
8 years	1 (100.0)	0 (0.0)
Seizure outcomes*		
>50% reduction	0 (0.0)	36 (100.0)
<50% reduction	15 (100.0)	0 (0.0)
Temporary improvement	1 (100.0)	0 (0.0)
Seizure free	0 (0.0)	4 (100.0)
Insufficient assessment period	18 (100.0)	0 (0.0)
No improvement	15 (100.0)	0 (0.0)
No follow-up	2 (100.0)	0 (0.0)
Worse	2 (100.0)	0 (0.0)
90% reduction	0 (0.0)	1 (100.0)
Weight at diet initiation		
<50th percentile	21 (60.0)	15 (40.0)
>50th percentile	3 (42.9)	4 (57.1)
50th percentile	29 (55.8)	23 (44.2)
Following diet at data collection		
Yes	9 (26.5)	25 (73.5)
No	44 (72.1)	17 (27.9)
Reasons for diet discontinuation[#]		
No improvement	13 (59.1)	9 (40.9)
The family not following a ketogenic diet	9 (42.9)	12 (57.1)
Adverse effects	9 (52.9)	8 (47.1)
Stopped following the ketogenic diet	5 (100.0)	0 (0.0)
Diet ratios		
1:1	3 (100.0)	0 (0.0)
2:1	5 (100.0)	0 (0.0)
3:1	30 (50.8)	29 (49.2)
4.5:1	15 (53.6)	13 (46.4)
Diet ratio changed*		
Yes	4 (28.6)	10 (71.4)
No	48 (60.0)	32 (40.0)
If the ratio changed, did patients show improvement*		
Diet was not changed	15 (75.0)	5 (25.0)
Yes	3 (50.0)	3 (50.0)
No	35 (51.5)	33 (38.5)

Data are presented as n (%). *, data was available for N=94. [#], reasons of discontinuing the diet were provided for N=65. SD, standard deviation.

Table 4 Univariate and multivariate logistic regression to assess factors contributing to decrease in seizures

Independent variables	Univariate logistic regression model			Multivariate logistic regression model		
	P value	Crude OR	95% CI of OR	P value	Adjusted OR†	95% CI of OR
Age (numerical variable)	0.206	1.053	0.972–1.140	0.103	1.076	0.985–1.175
Gender						
Female (ref.)		–			–	
Male	0.507	1.292	0.606–2.752	0.568	1.275	0.554–2.933
Weight						
50th percentile (ref.)		–			–	
<50th percentile	0.993	1.003	0.452–2.226	0.866	0.928	0.390–2.210
>50th percentile	0.496	1.739	0.354–8.549	0.635	1.487	0.289–7.645
Classification of seizures						
Spasm (ref.)		–			–	
Generalized	0.922	0.939	0.265–3.325	0.640	0.736	0.204–2.658
Focal	0.654	1.500	0.255–8.817	0.580	1.652	0.279–9.793
Medical history other than epilepsy	0.741	0.800	0.213–3.011	0.330	0.338	0.038–3.002
No (ref.)		–			–	
Still on diet	<0.001*	7.190	2.793–18.505	0.001*	6.277	2.210–17.826
Diet ratio changed	0.037*	3.750	1.082–12.995	0.041*	2.600	0.621–10.895
Physical activity level						
Spastic cerebral palsy (ref.)		–			–	
Wheelchair-bound	0.042*	4.167	1.053–16.484	0.279	2.383	0.494–11.495
Hypotonia	0.153	2.679	0.694–10.334	0.198	2.655	0.601–11.730
Ambulatory indoors and outdoors	0.001*	7.143	2.167–23.544	0.016*	4.996	1.350–18.489
Ambulatory indoors	0.076	3.571	0.874–14.602	0.435	1.939	0.368–10.203

Adjusted OR†, model adjusted for common confounders (type and KD duration of treatment, age at the time of the study, gender, weight, class of seizures, and presence of other medical conditions); *, P value is significant at P<0.05. CI, confidence interval; OR, odds ratio; KD, ketogenic diet.

showed improvement without changing the diet ratio. Thirteen out of 95 patients (14%) reached the end of the diet due to no improvement, seizure freedom for two years, inefficacy, inability for families to continue on diet, no compliance, and intolerance). We found that around 43% of children who did not improve on KD among those children whom families did not follow the KD although 57.1% showed improvement (*Table 3*).

Social determinants and parental factors (such as age, level of education, income, and access to health care) contributing to the decrease of seizures in patients on the KD were assessed in Table S1. Univariate regression analysis was conducted for parent-related factors to assess their contribution to the decrease in seizure frequency. None of the parental factors significantly increased or decreased the odds of seizures (all P values >0.05) (Table S2).

Univariate logistic regression analysis was conducted to assess the factors contributing significantly to the decrease in seizure frequency. Variables assessed were the type of treatment, age at the study, gender, weight, etiology of epilepsy, class of seizures, and presence of comorbidities. None of the studied factors were associated with a significant increase or decrease in the likelihood of seizure frequency (all P>0.05) (*Table 4*). Common confounders were adjusted

Table 5 Univariate and multivariate logistic regression to assess diet-related factors and physical activity contributing to the decrease in seizures

Independent variables	Univariate logistic regression model			Multivariate logistic regression model		
	P value	Crude OR	95% CI of OR	P value	Adjusted OR†	95% CI of OR
Still on KD						
No (ref.)		–			–	
Yes	<0.001*	7.190	2.793–18.505	0.001*	6.277	2.210–17.826
Diet ratio changed						
No (ref.)		–			–	
Yes	0.037*	3.750	1.082–12.995	0.041*	2.600	0.621–10.895
Physical activity level						
Spastic cerebral palsy (ref.)		–			–	
Wheelchair-bound	0.042*	4.167	1.053–16.484	0.279	2.383	0.494–11.495
Hypotonia	0.153	2.679	0.694–10.334	0.198	2.655	0.601–11.730
Ambulatory indoors and outdoors	0.001*	7.143	2.167–23.544	0.016*	4.996	1.350–18.489
Ambulatory indoors	0.076	3.571	0.874–14.602	0.435	1.939	0.368–10.203

Adjusted OR†, model adjusted for common confounders (sociodemographic factors, type and KD duration of treatment, age at the time of the study, gender, weight, class of seizures, and presence of other medical conditions.); *, P value is significant at P<0.05. CI, confidence interval; OR, odds ratio; KD, ketogenic diet.

in the regression model but no significant association was observed for any of the factors (all P values >0.05).

Table 5 shows crude and adjusted regression models assessing the patients' diet-related factors and physical activity on the decrease of seizures. Patients who continued the KD had seven times higher odds for decreasing seizure frequency compared to those who discontinued the KD [odds ratio (OR): 7.190, 95% CI: 2.793–18.505, P<0.001]. Patients with changed diet ratios had a 3.7-times probability for decreasing seizure frequency compared to patients with unchanged diet ratios (OR: 3.750, 95% CI: 1.082–12.995, P=0.037). Wheelchair-bound patients (OR: 4.167, 95% CI: 1.053–16.484, P=0.042) and patients ambulating indoors and outdoors (OR: 7.143, 95% CI: 2.167–23.544, P=0.001) had higher odds of improvement compared to patients with spastic CP. No other factors showed significant associations with seizure frequency.

Common confounders that could affect the decrease in seizures, including sociodemographic factors, type and duration of treatment, age at the time of the study, gender, weight, class of seizures, and presence of comorbidities were adjusted in the regression model. Continuing with the KD was significantly associated with decreased seizure frequency by six times more than those who discontinued the KD (OR: 6.277, 95% CI: 2.210–17.826, P=0.001). Patients ambulating indoors and outdoors had a five times higher probability of improvement than those with spastic CP (OR: 4.996, 95% CI: 1.350–18.489, P=0.016).

Discussion

Key findings

To the best of our knowledge, this is the first study in Saudi Arabia about children with refractory epilepsy on KD. This study also examined the social determinants and diet-related factors contributing to the decrease in seizures. Our findings suggest that KD is associated with reduced seizure frequency in children with refractory epilepsy. Our study participants were divided into two groups based on outcomes, participants who showed >50% reduction in seizure frequency were in the improved category and participants who showed <50% reduction or no reduction in seizures were in the not improved category. Lower improvements in seizure frequency in epileptic patients on ketogenic diets were associated with low education levels of parents (33.3% high school *vs.* 50% undergraduate school), low incomes (<11,400±7,560.864 SR), and diagnosis of seizures in patients >8 years old.

In Saudi Arabia, evidence of the effect of KD on the frequencies of seizures is scarce. The findings from previous studies about epilepsy in children in eastern and western Saudi Arabia had limitations, including a small sample size (8 children), conducted in one city, recall bias (outcomes measured by caregivers' recall); therefore, those findings should be interpreted with caution, as the sample size was small, and the observed effect of the KD might be underestimated; and the results cannot be generalized to the whole Saudi population (2). Another study conducted in Western Saudi Arabia region compared the effect of antiepileptic medications and KD on seizure outcomes (14). It showed that KD was effective in treating medically resistant epilepsy; however, their findings could be underestimated due to recall bias as the seizure outcomes were measured based on caregiver reports and subjective errors could be included in their collected data. In our study, however, we had a larger sample size and recruited children from a large referral center in the capital city (Riyadh), which is also a specialized center for epilepsy, and almost all cases who needed treatment with KD were referred to this center.

Strengths and limitations

A strength of this study is its sample size. We recruited 95 children from a large referral center in Riyadh that specializes in managing patients with refractory epilepsy who were using or had used KD for 12 months, as the decrease in seizure frequency can be expected with a longer duration of exposure to KD. This study considered the patients' sociodemographic variations and social determinants of health, and addressed and adjusted several confounding factors (such as sociodemographic characteristics, lifestyle, and KD related factors) in the statistical analysis.

This study has some limitations. There is missing data about the patients' parents' (or guardians') sociodemographic information, despite several attempts to contact them. However, sociodemographic factors were adjusted in the regression model to eliminate their effects on the association between the exposure to KD and decrease in seizure frequency. In Saudi Arabia, only a few large, specialized centers follow the KD protocol in managing children with seizures, which was an obstacle to recruiting a larger number of patients for this study.

Comparison with similar researches

Wilder first adopted the KD in 1921 and it has been used to treat refractory epilepsy for nearly 100 years (3,19). Its use globally inspired researchers when its beneficial effects were confirmed by several randomized trials (20,21); children on KD were up to three times more likely to be seizure free and up to six times more likely to have ≥50% reduction of seizures compared to children on regular treatment. Seizures in children with refractory epilepsy are uncontrolled with medications and these children have an increased risk of adverse effects, including cognitive impairment and kidney injury (22). These seizures affect their quality of life, if left uncontrolled (22); therefore, dietary therapy with KD has become a vital approach to decrease the seizures and improve the quality of life.

Explanations of findings

KD contains a very high fat and low carbohydrate content, reducing carbohydrates to <10% of used energy. This restriction triggers a systemic shift from glucose metabolism toward fatty acid metabolism yielding ketone bodies, such as acetoacetate and β-hydroxybutyrate as substrates for energy. The ketogenic diet provides sufficient protein for growth and development. Energy is mainly derived from fat in the diet and utilization of body fat. The KD is a biochemical model of fasting, which shifts organs to utilize ketone bodies instead of glucose as the energy source for the brain. The KD allows about 90% of the total caloric income from fat, 6% from protein, and 4% from carbohydrates (23).

This beneficial effect of KD was demonstrated in our study and could be explained by several mechanisms. The switch from carbohydrate-to lipid-based energy production significantly affects many biological processes (24). Ketones appear to provide a more efficient source of energy for the brain than glucose (3,24). Changes in neurotransmission, neuronal structure, and glial homeostasis combine to decrease seizure activity (25). Studies showed that ketones induce gene up-regulation resulting in an increase in neuronal and glial mitochondrial numbers; increased neuronal energy reserves lead to enhanced neuronal homeostasis and resilience (3,24,25). Additionally, studies have also found that a state of ketosis can raise levels of Gamma-aminobutyric acid (GABA) and reduce glutamate in the brain, preventing seizures. In addition, during

ketogenesis, the inhibitory neuropeptide Y (NPY) is increased which has antioxidative and anti-inflammatory effects. Thus, increased glutathione levels when on the KD, protects brain cells from damage by seizures induced elevated reactive oxygen species (ROS). Another mechanism might be due to histone deacylases epigenetic effect. Beta-hydroxybutyrate (BHB) is an inhibitor of class I histone deacylases, which facilitate epigenetic modification (25). Experimental research on mice showed that there is a protective effect of BHB against oxidative stress (26). Recent studies suggest that the kynurenine pathway likely plays a role in the neuroprotectant and anticonvulsive effects of the KD. Kynurenic acid has been found to be an endogenous neuroprotectant and antiepileptic agent (3,26).

Participants who started on 3:1 and 4.5:1 KD showed >50% reduction in seizure frequency. Participants who modified the diet ratio because of adverse effects of the previous ratio or lack of improvement in seizure frequency showed 50% reduction in seizure frequency. The participants who started on 3:1 KD showed better improvement and adherence as its lower fat content meant better tolerance. In the 3:1 diet group, 13.9% of the patients had GI symptoms, including nausea, vomiting, and diarrhea. GI disturbance is one of the main complications that is directly related to poor diet tolerance leading to KD discontinuation and reduction in the diet's positive effect (15). There were more improvements (around 50%) in patients who were on the 4.5:1 and 3:1 ratio KD, which are classic KD.

However, participants who followed a 1:1 and 2:1 ratio KD showed no improvement in seizure frequency compared to those who were started on 3:1 and 4.5:1 KD. However, there were only five patients who were following 2:1 ratio in our study, which might explain why these children have not shown a reduction in the frequency of seizures. According to Bahassan *et al.*, there were no differences between the efficacy of the medium chain triglyceride diet, which is a 1:1 ratio, compared to the classic KD. This finding could be underestimated due to their low sample size (N=8) and a poor limited follow-up (2).

The level of physical activity was significantly associated (P=0.001) with seizure frequency in children on KD. Patients ambulatory indoors and outdoors were about five times more likely to improve on KD compared with spastic CP patients (OR: 4.996, 95% CI: 1.350–18.489, P=0.016). Based on our results, the metabolic substrate changes during different activity levels and influences ketone body production (3); therefore, further research about the relationship between the KD and metabolic changes during different physical activity levels is needed, as there are limited studies about this relationship despite extensive epileptic studies. Therefore, KD require strict compliance and physical activity to maintain the metabolic changes.

Sociodemographic factors varied between the children on KD, which could affect its efficacy. We found that the age of onset of seizures affects the response to KD. Patients who had seizures aged ≤1 year showed more improvement than patients who were diagnosed aged >2 years. We included patients from infancy—14 years to compare the response in different age groups and found that age plays an important role in the response to KD. The incidence of epilepsy is greatest in the first 2 years of life when there is a poor prognosis for seizure control and neurodevelopmental outcomes (27), which could be the reasons KD works effectively in this age group. This is demonstrated as the children in this age group have fewer seizures than older children with epilepsy. A decrease in seizure frequency can be expected with longer use of the KD (23). Some studies have examined the effect of KD on different age groups and the duration of the KD (28); a study in China showed that age and duration of epilepsy have no significant effect on the KD efficacy (28); however, their findings could be underestimated due to a small sample size in each age group and a short follow-up (3 months).

Health-related quality of life can be regarded as the most important health outcome in any chronic health condition (29); patients whose parents (or guardians) had low incomes showed less improvement, which could be because families with low incomes are less able to get all the equipment and food supplements that support the KD treatment. Hospitals like KFMC supply families with only the basics of KD. In addition to the high cost of KD, most of our participants (52%) did not have private insurance to cover KD therapy expenses (such as weighing scales, and non-formula food products). However, patients receive a government disability benefit in the form of monetary funds. Health insurance coverage may not extend to the expenses of parents or guardians of patients with epilepsy in many countries, including Saudi Arabia. Private healthcare insurance is only mandatory for expats, Saudi nationals employed in the private sector, and their dependents (30). While healthcare in Saudi Arabia is free, the advent of privatization and implementation of health insurance policies may impact treatment coverage and access to healthcare. Additionally, KD products may not be readily available in all hospitals or pharmacies. We found that around 43% of children who did not improve on KD

among those children whom families did not follow the KD due to side effect or being on KD for more than 2 years or family cannot cope (*Table 2*). Most families complain about the extra effort needed for diet preparation (31) and several other cost-of-illness studies in combined populations of adults and children showed that service use and costs increase with more severe forms of illness and seizure frequency (32).

Females showed slightly more improvement in seizure frequency than males. The differences by sex for epilepsy and seizure susceptibility could be due to hormonal differences, which exhibit greater fluctuations in seizure susceptibility (33). However, evidence related to endocrinal and hormonal effects on epileptic patients, specifically children, is still in the early stages of research. Our results show that patients living outside Riyadh could better comply with the KD and consequently showed a decrease in seizure frequency. Although living in large cities can promote better access to healthcare, it can have a negative influence on the lifestyle and eating habits due to urban-rural differences (34), including many fast food restaurants and unhealthy diet options readily available and even delivered to the doorstep; urban children prefer to eat refined and sugary food instead of fresh fruits, vegetables, and protein. In contrast, living outside large cities promotes healthier eating habits and physical activity (34). Family function and status play a role in diet compliance and hence, we assume that according to our results, patients whose parents were divorced or widowed showed less improvement in seizure outcomes. The nature of epilepsy places a heavy burden on caregivers; therefore, the existence of both parents while on a KD is beneficial.

Patients on KD had seven times higher odds for decrease in seizures compared to those who discontinued the KD (OR: 7.190, 95% CI: 2.793–18.505, P<0.001). KD has fewer adverse effects and is cheaper than surgery (35,36).

Reduction of seizure frequency is high among KD users. While the seizure-free rates reported in most studies were modest (19), in randomized controlled trials, children on KD were up to three times more likely to have no seizures, and up to six times more likely to have reduced seizure frequency by ≥50% compared to children on regular treatment (21). Although surgical treatment is the gold standard approach, decrease in seizure frequency was higher among children who underwent surgery and had KD (37). Another possible explanation is that seizure semiology could play a part in the improvement of epileptic patients (7,28). When seizures are classified and compared, patients with generalized epilepsy (85.8%) had the highest improvements compared to those with focal and spasm epilepsy (7.1% and 7.1%, respectively).

Implications and actions needed

Although treating epileptic patients with KD has been implemented in many countries, its implementation in Saudi Arabia is restricted to a few large specialized centers. KD might be a promising alternative or adjunct to surgical resection and this information could be useful in seizure management.

Conclusions

We found up to 44% of refractive epilepsy patients had a decrease in seizures. They were on 3:1 and 4.5:1 ketogenic diets while patients on 1:1 and 2:1 ketogenic diets showed no decrease in seizure frequency. Patients with generalized epilepsy (78.3%) had the highest improvement in seizure outcomes. Patients ambulatory indoors and outdoors showed high levels of improvement (66.7%) compared to patients with CP (reference group). Less improvement in seizure outcomes was noted for epileptic patients on KD, if their parents had lower education levels, lower income levels, and were diagnosed with seizures aged >8 years.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tp.amegroups.com/article/view/10.21037/tp-23-211/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted according to the guidelines of the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of King Saud University College of Medicine (No. E-21-6123-CMED-305/F4), in agreement with the Institutional Review Board of the KFMC (No. 21-347E), after signing a material transfer agreement (MAT) by the provider at King Fahad Medical City. Data collected from hospital records but verbal informed consent from the patients' parents (or guardians) was obtained to complete the missing information from the medical records such as parents'/guardians' socioeconomic status (phone consent attached to Appendix 1).

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