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ORIGINAL ARTICLE

The effects of classic ketogenic diet on serum lipid profile in children with refractory seizures

Gholam Reza Zamani[1] · Mahmoud Mohammadi[1] · Mahmoud Reza Ashrafi[1] · Parviz Karimi[1] · Maryam Mahmoudi[1] · Reza Shervin Badv[1] · Ali Reza Tavassoli[1] · Reza Azizi Malamiri[2,1]

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Abstract More than 25 % of children with epilepsy develop refractory seizures unresponsive to both old and new generation anticonvulsants. Since such seizures have a serious negative impact on the quality of life, other treatment options are considered. The ketogenic diet is a well-known treatment for managing refractory seizures, although its mechanism of action is unknown. Studies have shown that this diet is as good as, or better than, any of the newer medications in reducing seizure frequency. However, concerns about adverse effects have been raised. We conducted an open label trial to show the effects of this diet on serum lipid profile. Thirty-three children with refractory epilepsy were treated with the ketogenic diet and were followed for 6 months. Their serum lipid profile was assessed at baseline, and at 3 and 6 months after initiating the diet. Seizure frequency was reduced in 63 % of children (no seizures in 2/33 and reduced >50 % in 19/33). However, after 6 months of administering the diet, median triglyceride was significantly increased (from 84 to 180 mg/dl, $P < 0.001$), median total cholesterol was significantly increased (from 180 to 285 mg/dl, $P < 0.001$), median serum low-density lipoprotein (LDL) was significantly increased (from 91 to 175 mg/dl, $P < 0.001$), and median serum high-density lipoprotein (HDL) was significantly increased (from 51 to 58 mg/dl, $P < 0.001$). Results of this study indicate that a classic ketogenic diet in children with refractory seizures is effective in seizure reduction, but leads to development of hypercholesterolemia and hypertriglyceridemia.

Keywords Children · Refractory seizures · Ketogenic diet · Serum lipid profile

Introduction

Although many pediatric epilepsies and epileptic syndromes are well-managed using both old and new generation anticonvulsants, more than 25 % of children with epilepsy develop refractory seizures, uncontrolled even with a combination of 3 or more properly selected anticonvulsive agents [1–3]. The negative impact of uncontrolled seizures on the quality of life of children and their parents has motivated the use of other treatments including epilepsy surgery and the ketogenic diet [4–6].

The ketogenic diet is a high fat, low carbohydrate and adequate protein diet that has been used for decades for the treatment of children with refractory seizures. The mechanism of the ketogenic diet in managing refractory seizures is unknown, but many pediatric studies have shown that the effect of this diet on seizure control is as good as, or better than, that of any of the newer medications [7]. Based on these findings, many tertiary pediatric epilepsy centers have developed ketogenic diet programs and clinics. After eight decades of administering the ketogenic diet, questions are now being raised about its adverse developmental effects [8–10].

The classic ketogenic diet dictates a 4:1 fat to carbohydrate ratio. Many of authorities prefer a 3:1 ratio plus adequate protein intake to ensure adequate growth in

✉ Reza Azizi Malamiri
azizi.ramin@gmail.com

[1] Paediatrics Centre of Excellence, Department of Paediatric Neurology, Children's Medical Centre, Tehran University of Medical Sciences, Tehran, Iran

[2] Department of Paediatric Neurology, Golestan Medical, Educational, and Research Centre, Ahvaz Jundishapur University of Medical Sciences, # 90, Golestan Blvd., P. O. Box 6135733118, Ahvaz, Iran

Table 1 Main studies reporting the effects of the ketogenic diet on plasma lipid profile and seizure frequency in children with refractory epilepsy

References	Sample size, [age range]	Type of diet	Follow-up time	Plasma lipids	Reduction in seizure frequency
Dekaban et al. [8]	11, [1 month to 6.5 years]	Classic 4:1	24 months	Significantly increased	5 became seizure free, more than 60 % reduction in 4
Chesney et al. [10]	45, [1–17 years]	Classic 4:1	10 months	Triglycerides and mean total cholesterol significantly increased	Not reported
Schwartz [9]	55, [1–20 years]	Classic 4:1, medium chain triglycerides (MCT), and modified MCT-some children treated with two types of diets	6 weeks	No significant change	More than 90 % in 26 treated with classic 4:1 diet, between 50% and 90 % in 25 treated with MCT, and less than 50 % in 12 treated with modified MCT
Katyal et al. [11]	42, [1–9 years]	Classic 3:1	350 days in half the patients	No significant change	More than 90 % in 16, 50–90 % in 14, and less than 50 % in 12
Kwiterovich et al. [7]	141, [1–20 years]	Classic 4:1 in 102, 3.5:1 in 7, and 3:1 in 32	All children for at least 6 months, in 59 at least 1 year, and in 27 at least 2 years	Total cholesterol, LDL, VLDL, triglycerides, and ApoB significantly increased	More than 50 % reduction in 93 (66 %) of children and in the rest of patients less than 50 %

children [7]. This fat to carbohydrate ratio has raised concerns about the effects of the ketogenic diet on total plasma cholesterol and triglyceride levels, and subsequent cardiovascular sequelae in children with refractory seizures [7]. Few studies have investigated the effects of the ketogenic diet on plasma lipid levels. Most studies conclude that the ketogenic diet is associated with increased plasma lipid levels in children [8, 10], but at least two studies showed opposing results [9, 11]. We have summarized the main findings of these studies in Table 1. Different sample sizes and methodologies may account for divergent results.

In our country, two major pediatric neurology centers have developed ketogenic diet programs and clinics to administer the diet in children with refractory seizures. Studies conducted in these centers have primarily focused on the effects of the diet on seizure control and adverse developmental effects. However, effects of the diet on plasma lipids remain unstudied. The current study thus aims to evaluate the effects of the classic 4:1 ketogenic diet on plasma lipid levels in children with refractory seizures and compare our results with the results of previous studies.

Methods

Study design and setting

We conducted an open label trial between January 2014 and July 2015, and administered a classic 4:1 ketogenic diet to children with refractory epilepsy. To evaluate the effects of a classic ketogenic diet on the serum lipid profiles, we obtained measures at baseline, and at 3 and 6 months after implementing the diet. Our epilepsy clinic is the second largest pediatric epilepsy clinic offering a ketogenic diet program. The program is directed by qualified nutritionists specialized in administering the ketogenic diet. The study design was approved by the Ethical Board Committee of the children's medical center and Tehran University of Medical Sciences. Written informed consent, approved by the Institutional Review Board, was obtained from the parents of participants before enrolment.

Subjects

We enrolled 33 children over the age of 2 years who suffered from refractory epilepsy and experienced at least two seizure episodes weekly while being treated with at least three properly selected anticonvulsant agents including at least one that was second or third generation. All children who were enrolled had acceptable serum anticonvulsant concentrations. Exclusion criteria were children younger than 2 years, children whose parents were reluctant to provide consent, children with primary carnitine deficiency, children with a family history of dyslipidemia and early cardiac death. We also excluded children with dilated cardiomyopathy, systemic hypertension, and systemic and metabolic diseases such as diabetes mellitus and obesity, because previous studies indicated harmful effects of

ketogenic diet in such conditions. We also excluded children due to non-compliance.

Pre-implementation procedure

Before diet implementation, interviews were conducted with all the children and their parents. A thorough history was taken and a precise systemic and neurologic exam was performed by the center's pediatric neurology staff. Children and their parents were educated about the diet and the effect of the diet on seizures. Parents were asked to record the frequency and severity of the seizures in a seizure diary 2 months prior to diet implementation and throughout the entire length of the study to assess efficacy. Children who adopted the diet were admitted. Prior to diet implementation, blood samples were obtained after an overnight fast, and echocardiography and renal ultrasonography were conducted. The following assessments were conducted to rule out possible metabolic diseases because our country does not offer routine neonatal metabolic screening: serum and urine organic acid profile, serum acylcarnitine profile, serum ammonia and lactate, venous blood gases, and a thorough serum metabolic screening by MS/MS method.

Diet implementation

Children enrolled into the study were admitted and fasted for 48 h. Their body weight and urine output along with serum and urine ketones were precisely monitored. Our center follows the Johns Hopkins ketogenic diet program [7]. After being released from the hospital, parents were asked to monitor their child's diet by checking urine ketones daily using urine dipsticks. All children were followed using hot lines (24/7 available mobile phones) and online social media (web-based support group using Telegram® social network). In all children, anticonvulsants were continued during administering the diet.

Patient follow-up and outcome measures

During monthly follow-up visits, we assessed seizure frequency and severity, and measured height and weight. Serum lipid profiles and triglycerides were measured at baseline, and at 3 and 6 months following diet implementation using enzymatic/colorimetric methods that are well described in previous studies [7, 12, 13].

Statistical methods

By using the prevalence of hyperlipidemia reported in previous studies [14] and accounting for 10 % lost to follow-up, we calculated a minimum sample of 31 patients, required to achieve 80 % power with Type I error $\alpha = 0.05$, and Type II error $\beta = 0.2$. All data were registered in prepared forms and entered into a computerized database. If quantitative data followed a normal distribution, we described measures using means and standard deviations, otherwise data were described using median and range. We used a repeated measure ANOVA to calculate differences in serum lipid profiles and triglycerides at the baseline, and at the third and sixth months after diet implementation. For data that were not distributed normally, we used the Kruskal–Wallis one-way ANOVA on ranks. In all statistical evaluations, $P < 0.05$ was considered significant.

Results

Baseline characteristics

Of the 33 children with refractory seizures who met the inclusion criteria, 25 were male and 8 were female, and the mean age was 6 years (±2.5, 2.5–10 years). Children presented with multiple seizure types including generalized tonic–clonic (GTC), atypical absence, tonic, clonic, myoclonic, and focal tonic and clonic seizures. Based on the age, etiology, seizure type, and epileptic syndrome, children were treated with a combination of at least three anticonvulsants including phenobarbital, phenytoin, carbamazepine, valproate, clobazam, nitrazepam, ethosuximide, primidone, vigabatrin, levetiracetam, prednisolone, and ACTH. Anticonvulsive medications were not changed during study. During the study, 25 children developed nausea, 23 developed constipation, and 2 developed diarrhea, but none of these complications resulted in the discontinuation of the diet.

Seizure frequency

Three months following diet implementation, seizures stopped in 2 of the 33 children, and seizure frequency decreased 75–90 % in 2 children, 50–75 % in 17, and 25–50 % in 7, compared to baseline measures. In 5 children, seizure frequency was unaffected by the change in diet. We thus considered the diet to be successful (>50 % seizure reduction) in 63 % (21/33) of children at 3 months. Six months after administering the diet, seizure frequency decreased 75–90 % in 6 children, 50–75 % in 15, and 25–50 % in 9 compared to baseline. In 3 children, seizure frequency was unaffected by the change in diet. The diet was thus successful in the same 63 % (21/33) of children after 6 months diet administration (Table 2).

Serum lipid profile and triglyceride levels

Median serum triglyceride and lipid levels over the study period are shown in Table 2. Primary analysis revealed that the data were not distributed normally. We thus present the data as median and range. Compared to baseline, serum triglyceride, serum total cholesterol, LDL, and HDL were all significantly increased 3 months after initiating the diet (P value <0.001). We found no significant changes between 3 and 6 months (Table 2).

Compared to a healthy pediatric population [15], 79 % of studied children demonstrated hypercholesterolemia (≥200 mg/dl), 64 % had high LDL levels (≥130 mg/dl), and 58 % had hypertriglyceridemia (≥100 mg/dl in 0–9 years and ≥130 mg/dl in 10–19 years) 6 months after diet implementation. Serum lipid profiles of all children are shown in detail in Table 3.

Discussion

In this study, we have shown that even though the diet successfully reduced seizure frequency by more than half in 63 % (21/33) of children, serum total cholesterol, LDL, and triglycerides significantly increased and a significant number of children in this cohort became hypercholesterolemic and hypertriglyceridemic. Evidence supporting these conclusions is that after 6 months of administering the diet, the median serum triglyceride increased from 84 to 180 mg/dl ($P < 0.001$), the median serum total cholesterol increased from 180 to 285 mg/dl ($P < 0.001$), and the median serum LDL increased from 91 mg/dl to 175 mg/dl ($P < 0.001$) (Table 2). Interestingly, over the study period and 6 months after initiating the diet, the majority of children demonstrated acceptable levels of serum HDL (>45 mg/dl) [15] (Table 2). Our results confirm findings from previous studies [7, 8, 10] indicating that the ketogenic diet significantly increases serum total cholesterol, LDL, and triglycerides.

Our results contribute to the growing body of evidence that plasma lipids and triglycerides increase in patients treated with the ketogenic diet [7, 8, 10]. Indeed both our study and a previous study with similar methodology [7] found a significant increase in plasma total cholesterol, LDL, triglycerides 6 months after initiating a classic 4:1 ketogenic diet in children with refractory seizures. In contrast, in our study, we did not observe the decrease in serum HDL described previously [7]. However, a second study with similar methodology [16] reported the same findings as ours: serum total cholesterol, LDL, and triglycerides significantly increased, and serum HDL remained constant over the study period. We believe the discrepancy in serum HDL levels may be accounted for by respective ethnic backgrounds of children across studies, different to ours in the former study [7], and similar to ours in the latter study [16].

We reviewed the methodology of those studies that reported no significant increase of triglyceride and serum lipids in children treated with the ketogenic diet [9, 11]. The best explanation for the discrepancy of findings between studies is the type of ketogenic diet employed. Katyal et al. [11] treated children using a classic 3:1 ketogenic diet and Schwartz et al. [9] treated three groups of children with different ketogenic diets (a classic 4:1, medium chain triglyceride (MCT), and MCT modified). Fat content in the diets administered in the first study and in a group of children in the second study is lower than the classic 4:1 ketogenic diet. This may explain why serum lipids were not significantly higher in either study [9, 11].

Previous studies in children and adults have claimed that increased levels of serum total cholesterol, LDL, triglycerides, and decreased level of serum HDL could lead to early cardiovascular death. Based on this knowledge, a number of studies were conducted to evaluate the short-term effects of the ketogenic diet on vascular function in children with refractory epilepsy [17–19]. None of these studies suggested that the ketogenic diet has a significant and long-lasting effect on carotid intima media thickness or on the elastic properties of the carotid artery and aorta. Moreover, even under the best conditions, a significant number of children with epilepsy refuse to continue the diet beyond 2 years because of the adverse events, including

Table 2 Seizure frequency and serum lipid profile over the study period

	Baseline	After 3 months	After 6 months	P value*
Weekly seizure frequency; median (range)	10 (2–60)	3 (0–10)	3 (1–10)	<0.001
Triglyceride (mg/dl); median (range)	84 (53–216)	183 (50–821)	180 (62–700)	<0.001
Total cholesterol (mg/dl); median (range)	180 (65–217)	280 (138–391)	285 (142–410)	<0.001
Serum LDL (mg/dl); median (range)	91 (67–222)	170 (80–336)	175 (71–258)	<0.001
Serum HDL (mg/dl); median (range)	51 (35–82)	59 (43–90)	58 (51–92)	<0.001

* P values by Kruskal–Wallis one-way analysis of variance on ranks between baseline and 3 and 6 months after administering the diet. No significant differences were found between 3 and 6 months after administering the diet

Table 3 Serum lipid profile and seizures count in children at baseline, 3 and 6 months after diet initiation

Patient number	Age in months	Sex	Triglyceride (mg/dl)			Total cholesterol (mg/dl)			LDL (mg/dl)			HDL (mg/dl)			Seizures count (weekly)		
			Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months	Baseline	3 months	6 months
1	93	M	85	326	280	135	391	350	82	275	229	48	43	61	8	8	8
2	48	F	167	231	242	190	231	268	86	153	151	35	49	51	2	2	2
3	112	M	88	181	173	205	181	286	132	192	187	49	61	59	10	10	10
4	59	M	67	80	79	147	169	153	67	90	84	68	60	62	10	10	5
5	84	M	65	76	70	143	154	142	77	80	71	49	52	54	5	5	4
6	68	M	74	81	85	195	183	176	96	102	98	69	53	57	10	8	8
7	74	F	97	183	192	189	183	261	116	148	152	56	55	57	10	7	7
8	65	M	60	352	340	180	390	230	110	150	140	52	68	65	3	2	2
9	73	F	191	821	700	165	336	321	80	192	202	52	50	58	5	3	3
10	67	M	88	59	62	65	110	169	152	120	99	73	61	53	5	3	3
11	82	M	80	287	279	140	342	330	91	251	221	39	47	52	2	1	1
12	128	F	123	231	227	179	231	259	115	161	161	52	56	55	2	1	1
13	67	F	68	173	180	183	173	325	92	219	219	79	65	67	5	2	4
14	216	M	216	203	180	213	361	340	222	270	250	61	54	55	8	3	3
15	38	M	53	140	130	217	280	252	120	180	160	41	56	58	12	4	1
16	60	M	112	340	560	178	370	410	125	336	241	38	59	57	10	3	3
17	81	M	70	135	135	190	280	285	83	170	175	82	83	82	15	4	1
18	81	M	70	135	135	190	280	285	83	170	175	82	83	82	5	1	1
19	37	M	94	50	85	190	210	230	90	110	120	50	90	92	15	3	3
20	122	M	56	138	141	139	138	254	78	167	166	51	48	53	10	2	2
21	35	M	87	245	240	156	310	303	92	175	181	44	65	58	6	1	1
22	65	M	60	352	340	180	390	230	110	150	140	52	68	65	20	3	3
23	47	F	97	152	148	192	347	314	105	210	200	67	70	69	20	3	3
24	82	M	80	287	279	140	342	330	91	251	221	39	47	52	15	2	2
25	37	M	94	50	85	190	210	230	90	110	120	50	90	92	10	1	1
26	81	M	70	135	135	190	280	285	83	170	175	82	83	82	10	1	1
27	60	M	112	340	560	178	370	410	125	336	241	38	59	57	20	2	2
28	82	M	80	287	279	140	342	330	91	251	221	39	47	52	30	3	3
29	53	F	84	161	164	150	161	295	88	207	258	51	57	58	10	1	1
30	44	F	73	220	228	138	190	201	68	87	112	42	54	81	60	5	5
31	65	M	60	352	340	180	390	230	110	150	140	52	68	65	20	1	1
32	37	M	94	50	85	190	210	230	90	110	120	50	90	92	50	0	4
33	60	M	112	340	560	178	370	410	125	336	241	38	59	57	20	0	1

M male, *F* female

gastrointestinal side effects. Based on the results of studies about the cardiovascular effects of the ketogenic diet, hypercholesterolemia and hypertriglyceridemia will be expected as known side effects of the treatment with unknown long-lasting effects.

This study had a number of limitations, which should be considered. This is a single center study with a small sample size. Logistics prevented the long-term follow-up of children and thus the long-term effects of the ketogenic diet remain unknown. Because of small sample size we could not determine a correlation between antiepileptic medications or type of seizures and serum lipid profiles.

In conclusion, results of this study indicate that a classic 4:1 ketogenic diet in children with refractory seizures is effective for seizure control, but could lead to development of hypercholesterolemia and hypertriglyceridemia over the course of treatment. Unfortunately, none of the studies in children, including our study, followed up the children for a long enough period to show the delayed effects of this treatment on the function of the cardiovascular system. Therefore, long-term cohort studies are warranted to evaluate the delayed effects of the ketogenic diet in children.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study design was approved by the Ethical Board Committee of the children's medical center and Tehran University of Medical Sciences.

Informed consent Written informed consent, approved by the Institutional Review Board, was obtained from the parents of participants before enrolment.

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