Neurol Sci (2016) 37:465–470
DOI 10.1007/s10072-015-2436-2

ORIGINAL ARTICLE

The effect of olive oil-based ketogenic diet on serum lipid levels in epileptic children

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Received: 6 August 2015 / Accepted: 2 December 2015 / Published online: 23 December 2015

Abstract Ketogenic diet (KD) is one of the most effective therapies for intractable epilepsy. Olive oil is rich in monounsaturated fatty acids and antioxidant molecules and has some beneficial effects on lipid profile, inflammation and oxidant status. The aim of this study was to evaluate the serum lipid levels of children who were receiving olive oil-based KD for intractable seizures at least 1 year. 121 patients (mean age 7.45 ± 4.21 years, 57 girls) were enrolled. At baseline and post-treatment 1, 3, 6, and 12 months body mass index-SDS, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels were measured. Repeated measure ANOVA with post hoc Bonferroni correction was used for data analysis. The mean duration of KD was 15.4 ± 4.1 months. Mean total cholesterol, LDL-cholesterol and triglyceride levels were significantly higher at 1st, 3rd, 6th and 12th months of the KD treatment, compared to pre-treatment levels ($p = 0.001$), but showed no difference among during-treatment measurements. Mean body mass index-SDS and HDL-cholesterol levels were not different among the baseline and follow-up time points ($p = 0.113$ and $p = 0.067$, respectively). No child in this study discontinued the KD because of dyslipidemia. Even if rich in olive oil, high-fat KD causes significant increase in LDL-cholesterol and triglyceride levels. More studies are needed to determine the effect of KD on serum lipids in children using different fat sources in the diet.

Keywords Children · Epilepsy · Olive oil · Ketogenic diet · Cholesterol · Triglyceride

Introduction

The ketogenic diet (KD) is a high-fat, adequate protein and low-carbohydrate diet that mimics the metabolic state of long-term fasting. It induces generation of ketone bodies by ketogenesis in the mitochondrial matrix of liver cells from which ketone bodies are subsequently exported to other organs such as brain tissue [1]. Fat content in the KD supplies 70–90 % of the calories, while the rest of the energy comes from protein and carbohydrates, but the ratio of fat content to protein and carbohydrates can be adjusted based on individual need of the patient.

Ketogenic diet is one of the most effective therapies for intractable epilepsy in both adult and pediatric population [2–5]. On the other hand, KD can cause adverse effects such as impaired linear growth [6], constipation [7], selenium deficiency and cardiomyopathy [8], kidney stones [9] and hyperlipidemia [9–12]. Although, risk for coronary artery disease or cerebrovascular disease may increase with

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long-term elevations of total and low-density lipoprotein (LDL)-cholesterol levels, previous pediatric studies showed no change in the carotid intima-media thickness compared to baseline and 6th and 24th months of therapy [12–14]. Nevertheless, long-term vascular outcomes of this highly fatty diet are not known yet.

Long-chain triglyceride-based classical KD, medium-chain triglyceride-based KD, modified Atkins diet and lastly, low-glycemic index containing KD are the most common KD modalities in the world [15, 16]. Nevertheless, hyperlipidemia is still common with these diets which have different fat ratios and different fat sources [9–12]. On the other hand, olive oil is rich in monounsaturated fatty acids and antioxidant molecules, mainly phenolic compounds. It has positive effects on lipid profile, inflammation and oxidant status [17–19], it prevents LDL oxidation and lipid peroxidation [20], stimulates antioxidant capacity of vitamin E [21] and also nonenzymatic antioxidant capacity [22]. We aimed with this study to determine the effect of olive oil consumption on serum lipid levels in multidrug-resistant epileptic children when treating with olive oil-based KD.

Methods

Patients and setting

This study performed at the Behçet Uz Pediatric Research and Training Hospital, Izmir, Turkey. Patients who were seen for medically refractory epilepsy at Pediatric Neurology Department were placed on KD. All patients were admitted to the hospital for initiation of the KD. Out of 320 patients who were initiated on KD, patients who stayed on KD for at least 12 months were enrolled. Inclusion criteria were: (1) children or adolescents with at least two seizures per week despite the appropriate use of at least two antiepileptic drugs, (2) strict compliance to the KD and attendance to all required follow-up clinic visits and (3) no previous use of the KD. Exclusion criteria were: (1) use of medications other than antiepileptic drugs such as steroids, fish oils or carnitine, etc., (2) give blood samples before 12-h fasting period, (3) impaired liver functions before KD initiation and (4) parents' non-approval.

Dietary protocol

All children were started on a 3:1 or 4:1 ketogenic diet ratio (Table 1). The initial calorie need was calculated individually for each patient according to the energy requirements for ideal body weight calculated by baseline height and the level of physical activity of each patient. During the diet's initiation, patients were hospitalized and monitored for any acute side effects. Blood glucose and ketone concentrations were measured twice daily until blood ketone concentrations stabilized between 4 and 5 mmol/L. When the goal calorie and diet ratio was achieved, the child was discharged home. Patients were followed-up by e-mail, and blood ketone and any adverse event were reported daily by parents to the treating physician. Ketogenic diet ratio was adjusted according to the blood ketone concentrations and degree of seizure control. The caloric intake was adjusted to maintain an ideal body weight for height based on the patient's weight gain or loss on the KD.

Table 1 Baseline characteristics of the patients ($n = 121$)

Characteristics	No (%)
Sex (male/female)	64/57
Etiology	
Idiopathic	30 (24.7)
Perinatal asphyxia	14 (11.5)
Cortical dysplasia	13 (10.7)
Neurocutaneous syndromes	13 (10.7)
GLUT-1 deficiency	7 (5.7)
Dravet syndrome	5 (4.1)
Other	39 (32.1)
Fat/protein plus carbohydrate ratio	
1:1	0 (0.0)
2:1	0 (0.0)
3:1	104 (85.9)
4:1	17 (14.1)
Nasogastric tube-feeding in addition to oral nutrition	11 (9.0)

GLUT-1 Glucose transporter protein-1

The recipes were planned considering the families and child's preferences. The menus were prepared according to Turkish traditional foods to increase patient's compliance and palatability. A Mediterranean style ketogenic diet was prepared which particularly contains extra virgin olive oil as the principal monounsaturated fat source. Mean olive oil amount was 80–85 % of total fat content of the meal. Other fat sources were cream (for specially to make ice-cream), meats and butter (for using to make soups) (Table 2). Palm oil, sunflower oil, hazelnut oil, coconut oil or corn oil was not used. We did not use high-fat content formula to feed the patients who had nasogastric tube.

Data collection and variables

Demographics, type of seizure, epilepsy syndrome, etiology, electroencephalography and neuroimaging findings were recorded during the baseline and follow-up clinic visits. Follow-up clinic visits were scheduled at 1, 3, 6 and 12 months after the KD initiation. Anthropometric

Table 2 Recommended foods and fats for patients

Food groups	Recommended	Not recommended
Meat, egg	Skinless chicken or turkey, lean beef, fish, egg yolk[a] or white	Chicken or turkey skin, shellfish
Fat and nuts	Olive oil (80–85 % of total fat content of the meal), butter[a], olive, walnuts, hazelnuts, almonds	Palm oil, sunflower oil, hazelnut oil, coconut oil, corn oil, margarine
Milk, dairy products	Milk, cream[a], yogurt, cheese	

[a] If hyperlipidemia occured in a patient, this food was excluded from the diet

features, gastrointestinal symptoms, method of feeding, seizure frequency, adverse events, compliance with the diet and biochemical parameters were recorded at baseline, and at each follow-up visits. The body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). A BMI-SDS was calculated and recorded.

Biochemical parameters

Blood was obtained by venipuncture in the forearm in the morning after an overnight fast. Standard tubes without anticoagulant were used for biochemical analysis. Samples were centrifugated at 3000 *g* in 4 °C for 15 min. Blood glucose, serum creatinine, blood urea nitrogen, liver function tests (albumin, bilirubin, alanine and aminotransferase), total cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride were analyzed. Low-density lipoprotein cholesterol level was calculated using the Friedewald formula in samples with a triglyceride level of less than 400 mg/dL (LDL-cholesterol = total cholesterol − HDL-cholesterol − triglycerides/5) [23]. Dyslipidemia was defined as total cholesterol >200 mg/dL, triglyceride >130 mg/dL, LDL-cholesterol >130 mg/dL and HDL-cholesterol <35 mg/dL at each visits [11].

Dietary interventions for hyperlipidemia

If a patient was diagnosed with hyperlipidemia and baseline or at any stage of the diet, we modified the diet to (1) reduce dietary fats by 20–25 % without effecting blood ketone levels and seizure control efficacy, (2) eliminate egg yolk from the diet and (3) eliminate the saturated fats (cream, butter, fatty meats) from the diet.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences version 15.0. Continuous and categorical variables were reported using mean ± standard deviation and number (%), respectively. Univariate repeated measures ANOVA with a Greenhouse–Geisser correction was performed to analyse the lipid changes of the patients with time (prior to, and at 1, 3, 6 and 12 months after KD treatment). To identify the source of significant differences among means, post hoc analysis was performed using the Bonferroni test. The significant level for post hoc multiple comparisons was set at 0.005.

Results

Out of 320 patients who were on KD, 121 patients [mean age 7.45 ± 4.21 years (2–18 years), 57 girls (47.1 %)] were enrolled. Table 1 summarizes baseline characteristics of the patients and etiology of the seizures. Etiology could not be determined in 30 patients (24 %). All patients were on multiple antiepileptic drugs, including phenobarbital, valproic acid, carbamazepine, oxcarbazepine, levetiracetam, topiramate, benzodiazepines, clobazam, primidone and zonisamide. Number of antiepileptic drugs decreased as the seizure control was achieved; median drug number was three at the beginning of the KD, two at the 1st and 3rd months, and one at the 6th month. Chewing and swallowing difficulties were reported in 59 patients (48 %) at the admission. Eleven patients (9.0 %) were also feeding via nasogastric tube in addition to oral nutrition.

The mean duration of KD was 15.4 ± 4.1 months. 24 months was maximum duration of follow-up on the KD (12 patients). Initial KD ratio was 3:1 in 104 children (85.9 %) and 4:1 in 17 children (14.1 %) (Table 1). At 12th months of the treatment, only two children (1.6 %) were on 4:1 ratio, 49 children (40.4 %) on 3:1 ratio, 45 children (37.1 %) on 2:1 ratio and 25 children (20.6 %) on 1:1 ketogenic diet ratio. Seizure control improved in totally 96 patients (79.3 %) at the end of the 12 months. A greater than 50 % decrease in seizure frequency while on the diet was observed in 37 patients (30.5 %) and complete seizure control was achieved by 59 patients (48.7 %).

Mean total cholesterol, LDL-cholesterol and triglyceride levels were significantly higher at 1st, 3rd, 6th and 12th months of the KD treatment compared to baseline levels (Tables 3 and 4). On the other hand, there was no difference in the total cholesterol, LDL-cholesterol and triglyceride levels among 1st, 3rd, 6th and 12th months of the treatment. Mean BMI-SDS and HDL-cholesterol levels were not different across baseline and during treatment

Table 3 Anthropometric values and total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels of patients at baseline and during ketogenic diet treatment (mean ± SD)

Parameter	Baseline	1st month	3rd month	6th month	12th month	*p* value*
BMI	16.6 ± 3.4	16.5 ± 3.1	16.4 ± 2.9	16.5 ± 2.5	16.2 ± 2.2	0.755
BMI-SDS	−0.39 ± 1.7	−0.41 ± 1.6	−0.42 ± 1.6	−0.43 ± 1.5	−0.45 ± 1.6	0.113
TC (mg/dL)	177.8 ± 35.3	217.7 ± 59.0	216.2 ± 63.1	211.4 ± 58.6	201.2 ± 54.1	0.001
LDL-C (mg/dL)	106.2 ± 33.0	131.9 ± 52.8	126.7 ± 47.8	123.1 ± 42.9	120.9 ± 43.1	0.001
HDL-C (mg/dL)	54.5 ± 17.6	55.8 ± 17.3	53.4 ± 15.5	52.2 ± 14.8	55.9 ± 15.8	0.067
TG (mg/dL)	89.3 ± 34.1	124.2 ± 71.7	135.2 ± 116.6	132.5 ± 105.0	111.0 ± 66.2	0.001

TC total cholesterol, *LDL-C* low density lipoprotein cholesterol, *HDL-C* high density lipoprotein cholesterol, *TG* triglyceride

* Univariate repeated measures ANOVA was used

Table 4 Dyslipidemia in patients at baseline and during ketogenic diet (n = 121)

Serum lipids	Baseline, *n* (%)	1st month, *n* (%)	3rd month, *n* (%)	6th month, *n* (%)	12th month, *n* (%)
TC >200 mg/dL	31 (25.6)	69 (57.0)	62 (51.2)	61 (50.4)	43 (35.5)
LDL-C >130 mg/dL	22 (18.2)	46 (38.0)	46 (38.0)	46 (38.0)	38 (31.4)
HDL-C <35 mg/dL	12 (9.9)	7 (5.8)	11 (9.1)	8 (6.6)	6 (5.0)
TG >130 mg/dL	17 (14.0)	35 (28.9)	40 (33.1)	41 (33.9)	28 (23.1)

TC Total cholesterol, *LDL-C* low density lipoprotein cholesterol, *HDL-C* high density lipoprotein cholesterol, *TG* triglyceride

period ($p = 0.113$ and $p = 0.067$, respectively). No child in this study discontinued the KD because of dyslipidemia.

Discussion

The most important finding of this study is increased total cholesterol, LDL-cholesterol and triglyceride levels at 1st, 3rd, 6th and 12th months of the diet in children with intractable epilepsy who were treated with olive oil-based KD. To our knowledge, this is the first study reporting the effect of olive oil-based KD on the serum lipids in children with medically refractory epilepsy.

We used olive oil as the main fat source of the KD in epileptic patients with the hypothesis that olive oil decreases the risk of KD associated hyperlipidemia. This was based on the previous studies that showed consumption of oliveoil is associated with decreased lipid levels other than HDL-cholesterol [18, 19] and diminished risk of atherosclerosis [24, 25]. Our findings showed that even oliveoil-based KD caused hyperlipidemia as early as the first month of treatment. This elevation in serum level, however, stabilized during the follow-up period and showed a trend to decrease at the 12th month visit although it was not statistically significant. This finding is interesting because oliveoil is known to have positive effect on serum lipids based on previous studies and requires further research to understand the hyperlipidemic mechanism of olive oil in KD.

Elevated total cholesterol, LDL-cholesterol and triglyceride levels have been documented in children on KD in previous studies [9–12]. For example, in a prospective study, Kwiterovich et al. [10] showed a significant increase in serum levels of total cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides and apolipoprotein B; a significant decrease in HDL-cholesterol at 6th months. These changes remained significant in 12th, and 24th months' follow-up compared to baseline levels, but the mean levels of total and LDL-cholesterol were lower than 6th month's levels. Additionally, the percentage of the patients with abnormal serum lipid levels was higher up to 60 % during follow-up periods [10] which is a finding that was repeated later by another study from the same center [11]. Compared to these studies, the rate of dyslipidemia was lower in our patient groups. Similarly, the mean difference of the serum lipid levels at 6th month follow-up was lower in our study. In addition to that, only 14 % of our patients had 4:1 KD ratio at the initiation phase which decreased to about 2 % at 12th month follow-up. However, this rate was 53–72 % in the previous studies [10, 11]. Although a direct comparison between these studies and our study cannot be done, these findings might be related to a positive effect of the olive oil on serum lipids. Further studies comparing KD with different fat sources are required to determine if such an effect is present.

Different strategies that have been employed for the KD-induced hyperlipidemia include medium-chain triglyceride

oil substitution, polyunsaturated fat substitution, decreased KD ratio or addition of carnitine [11]. Nevertheless, improvement in dyslipidemia was achieved in almost 50 % of the patients with cholesterol level >200 mg/dL; in 60 % with intervention and in 40 % without intervention [11]. In another study, Liu et al. [26] showed that even baseline hyperlipidemia can be managed during KD therapy by excluding all fatty meats, egg yolk, cream, butter, animal fat and palm and coconut oil from the KD, and adding omega 3 fatty acids or carnitine supplementation. Even though we did not use palm-coconut, other oils, carnitine, fish oil or lipid-lowering drugs in our study, the rate of patients with abnormal serum lipids decreased from 29 to 57 % at 1st month to 23–35 % at 12th months after the diet. Additional interventions that we did not employ may be expected to decrease these rates even further.

Decreased KD ratio can be another option for treating hyperlipidemia. Cervenka et al. [27] showed that epileptic adult patients treated with modified Atkins diet (approximately a 1:1 KD ratio) have similar total, HDL- and LDL-cholesterol and triglyceride levels at baseline and after 12 months of KD treatment. We initiated KD with 3:1 ratio in majority of the patients. This ratio was further reduced in most of the patients due to high blood ketone concentrations during follow-up. At the end of the first year 58 % of the patients achieved desired blood ketone levels with only 2:1 or lower KD ratios which also could be another factor for the trend of lower totalcholesterol, LDL-cholesterol and triglyceride levels at the 12th month compared to previous follow-up periods. Longer follow-up studies with higher patient numbers are needed to determine the effect of diet ratio on the serum lipid levels.

Our study has limitations. First limitation is the relatively small sample size of the study group. Second limitation is the short follow-up period of the patients. Third, we did not have any comparison group such as patients with classical KD. A new study can compare olive oil-based KD with classical KD regarding lipid levels of the patients. Lastly, the possible confounding effect of antiepileptic drugs on serum lipids could not be eliminated in our study [28–30].

In conclusion, high-fat ketogenic diet, even if had oliveoil, produced significant increases in LDL-cholesterol and triglyceride levels. Further comparative prospective studies with larger sample size and longer follow-up durations are needed to determine the effects of different fat source-based ketogenic diets on lipid profiles in patients with intractable epilepsy.

Acknowledgments We thank all the patients and parents who contributed to this study.

Compliance with ethical standards

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

Ethical approval The study protocol was designed in compliance with the 1964 Declaration of Helsinki. Informed consent was obtained from parents on enrollment in the study. The study was started and data collection began after the approval of the Ethics Committee of the Dokuz Eylul University Faculty of Medicine (Number of ethical approval: 2015/10-38).

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