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Is ketogenic diet treatment hepatotoxic for children with intractable epilepsy?

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ABSTRACT

Purpose: Long-term ketogenic diet (KD) treatment has been shown to induce liver steatosis and gallstone formation in some *in vivo* and clinical studies. The aim of this retrospective study was to evaluate the hepatic side effects of KD in epileptic children.
Method: A total of 141 patients (mean age: 7.1 ± 4.1 years [2–18 years], 45.4% girls), receiving KD at least one year for intractable epilepsy due to different diagnoses (congenital brain defects, GLUT-1 deficiency, West syndrome, tuberous sclerosis, hypoxic brain injury, etc.) were included in the study. Serum triglyceride, cholesterol, aminotransferase, bilirubin, protein and albumin levels and abdominal ultrasonography were recorded before and at 1, 3, 6, and 12 months following after diet initiation.
Results: The mean duration of KD was 15.9 ± 4.3 months. At one month of therapy, three patients had elevated alanine and aspartate aminotransferase levels. These patients were receiving ketogenic diet for Doose syndrome, idiopathic epilepsy and GLUT-1 deficiency. Hepatosteatosis was detected in three patients at 6 months of treatment. Two of these patients were treated with KD for the primary diagnosis of tuberous sclerosis and one for Landau Kleffner syndrome. Cholelithiasis was detected in two patients at 12 months of treatment. They were receiving treatment for West syndrome and hypoxic brain injury sequelae.
Conclusion: Long-term ketogenic diet treatment stimulates liver parenchymal injury, hepatic steatosis and gallstone formation. Patients should be monitored by screening liver enzymes and abdominal ultrasonography in order to detect these side effects.

1. Introduction

Ketogenic diet (KD) is a high fat, low-carbohydrate, adequate protein diet which has been extensively used for the treatment of intractable epilepsy [1,2]. Although the exact mechanisms of action remain unclear, basic studies indicate that several mechanisms may be involved in the effects of ketogenic diet, including disruption of glutamatergic synaptic transmission, inhibition of glycolysis, alteration of mitochondrial permeability and activation of ATP-sensitive potassium channels by mitochondrial metabolism [3–5].

The diet has been shown to be effective in clinical studies, and more than 50% of treated children have achieved seizure reductions of more than 50% [6–8]. On the other hand, KD may cause some metabolic and gastrointestinal adverse effects such as hyperlipidemia [9,10], hypoglycemia [11], pancreatitis [12], nausea/vomiting [13], diarrhea and/or constipation [13,14], protein-losing enteropathy [15] and hypoalbuminemia [16] in addition to other common acute or chronic complications. Ketogenic diet treatment has been shown to cause toxic effects in the liver in some animal studies [17–23]. Moreover, long-term KD treatment may stimulate hepatitis as well as gallstone formation in epileptic patients [13,16,24,25]. The aim of this retrospective study was to evaluate the hepatic side effects of KD in epileptic children.

2. Methods

2.1. Study population

This study was carried out at Behçet Uz Pediatric Research and Training Hospital, Izmir, Turkey between June 2013 and January

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2016. Patients with intractable epilepsy who remained on KD for at least 12 months were enrolled. Inclusion criteria were: (a) children or adolescents with at least two seizures per week despite the appropriate use of at least two antiepileptic drugs; (b) strict compliance to KD and attendance to all required clinic visits for follow-up; (c) no previous use of KD; (d) no previous liver disease; (e) no family history of liver disease. One patient who had an existing gallstone prior to the beginning of ketogenic diet was excluded. Other exclusion criteria were: (a) use of medications other than antiepileptic drugs such as steroids, fish oils, antibiotics or carnitine *etc.*; (b) elevation of liver enzymes by two-fold of upper normal limits before KD initiation; (c) parents' non-approval. Finally, 141 children were enrolled in the study.

2.2. Dietary protocol

The children were admitted to the hospital for KD initiation using a non-fasting gradual initiation protocol. The ketogenic diet ratio [fat/(protein plus carbohydrate)] was gradually increased to 3:1 or 4:1 in four days according to the patients' blood ketone levels. The initial calorie need was calculated individually for each patient according to the energy requirement for ideal body weight calculated by baseline height and the level of physical activity of each patient. All ketogenic diets were formulated on an individual basis with regard to the child's current food choices. A Mediterranean style ketogenic diet was prepared which particularly contained extra virgin olive oil as the principal fat source and included common locally available food as described previously [26].

During the diet initiation, patients were hospitalized and monitored for any initial adverse effects. Blood glucose and beta hydroxy butyric acid concentrations were measured twice daily until blood beta hydroxy butyric acid levels stabilized between 4 and 5 mmol/L. When the target energy and diet ratio was achieved, the child was discharged from the hospital. Patient follow-up was conducted by e-mail; blood ketone levels, seizure frequency and dietary compliance as well as all adverse events 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 during the KD. The minimum protein intake provided for children in prepubertal ages was 1 g/kg/day and was adjusted according to serum protein and albumin levels.

2.3. Data collection and variables

Demographics, type of seizure and etiology were recorded at baseline. Anthropometric features, seizure control, side effects, compliance to the diet were assessed; and laboratory investigations and abdominal ultrasonography examinations were recorded before and after 1, 3, 6, and 12 months of therapy. The body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). A BMI-SDS was calculated and recorded. The seizure control was categorized as follows: seizure free, >50% seizure reduction or <50% seizure reduction.

2.4. Biochemical parameters

Blood was obtained by venipuncture from the forearm in the morning after an overnight fasting. Standard tubes without anticoagulant were used for biochemical analysis. Liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, total and direct bilirubin, gamma glutamyl transpeptidase (GGT), alkaline phosphatase (ALP)], total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides 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) [27]. Normal ranges of laboratory values were evaluated according to *Nelson Textbook of Pediatrics, 19th edition* [28]. A value of 45 U/L was accepted as the upper normal limit for ALT levels in children from one month to 19 years of age. Values of 60 U/L and 50 U/L were accepted as upper normal limits for AST levels in children aged 1–3 years and above 3 years of age, respectively [28]. 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 visit [9,26].

2.5. Ethical approval

The study protocol was designed in compliance with the 1964 Declaration of Helsinki. Informed consent was obtained from parents upon enrollment in the study. The study was initiated and data collection was performed after the approval of the Ethics Committee of Dokuz Eylul University Faculty of Medicine (Number of ethical approval: 2015/20-13).

2.6. Statistics

Data were recorded with Statistical Package for Social Sciences version 15.0. Continuous and categorical variables were reported as mean ± standard deviation and number (%), respectively.

3. Results

3.1. Demographic features

A total of 141 children with KD duration ≥12 months were included, 64 (45.4%) of which were girls; and mean age at seizure onset was 0.9 ± 1.8 years (median 1.1 years, from 1 month to 9 years). The mean age at KD initiation was 5.6 ± 4.2 years (median 5 years, 1–18 years). The mean duration of KD was 15.9 ± 4.3 months. Mean age of the children was 7.1 ± 4.1 years at enrollment to the study.

Various seizure etiologies were identified among the 107 children, including hypoxic ischemic encephalopathy (n = 24, 17%), cortical dysplasia (n = 17, 12.1%), tuberous sclerosis (n = 16, 11.3%), idiopathic West syndrome (n = 10, 7.1%), glucose transporter protein-1 (GLUT-1) deficiency (n = 7, 5.0%), Dravet syndrome (n = 5, 3.5%), Herpes encephalitis (n = 5, 3.5%), Lennox–Gastaut syndrome (n = 4, 3.5%) and other etiologies (n = 19, 13.4%). Etiology could not be determined in 34 patients (24.1%).

Before KD treatment, children had tried a mean of 3.1 ± 1.1 (median 3 drugs) anticonvulsant drugs including phenobarbital, valproic acid, carbamazepine, oxcarbazepine, levetiracetam, topiramate, benzodiazepines, clobazam, primidone, and zonisamide. The number of antiepileptic drugs were decreased as seizure control was achieved; median drug number was two at 1 and 3 months, and one at 6 months.

Initial KD ratio was 3:1 in 124 children (88.0%) and 4:1 in 17 children (12.0%). At 12 months of treatment, the KD ratio was 4:1 in only 2 children (1.4%), 3:1 in 58 children (41.1%), 2:1 in 56 children (39.7%), and 1:1 in 25 children (17.8%). Outcome of KD was as follows: 67 (47.5%) patients became seizure free; 55 (39.0%) had >50% decrease in seizures; and 19 (13.5%) patients had <50% decrease in seizures.

3.2. Patients with hepatic side effects

Initially, all participants had normal serum values in liver function tests and no fatty liver at ultrasonography. Hepatic side