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Can Children With Hyperlipidemia Receive Ketogenic Diet for Medication-Resistant Epilepsy?

Yeou-Mei Christiana Liu, MSc[1], Helen Lowe, MSc[1], Maria M. Zak, MN[1], Jeff Kobayashi, MD[1], Valerie W. Chan, BScN[1], and Elizabeth J. Donner, MD[1]

Abstract

The very-high-fat ketogenic diet can worsen lipid levels in children with pre-existing hyperlipidemia by increasing serum lipoproteins and reducing antiatherogenic high-density lipoproteins. A retrospective chart review of 160 children treated with the ketogenic diet from September 2000 to May 2011 was performed. Twelve children with pre-existing hyperlipidemia were identified. Lipid levels including total cholesterol, low-density lipoprotein, triglycerides, high-density lipoprotein, and total cholesterol/high-density lipoprotein were measured pre-diet and at 3, 6, and 12 months of treatment. During treatment, there was a significant reduction in mean total cholesterol, low-density lipoprotein, and total cholesterol/high-density lipoprotein. Total cholesterol and low-density lipoprotein were normalized in 8 and 7 children at 6 months; and 9 and 9 children at 12 months respectively. At 6 and 12 months, tot cholesterol/HDL ratio was normalized in 5 and 7 children respectively. Diet modifications were made to achieve healthy lipid levels. By extrapolating the data, it suggests lipid levels can be controlled in children and adults with ketogenic diet treatment.

Keywords

hyperlipidemia, ketogenic therapy, total cholesterol, low-density lipoprotein, total cholesterol/high-density lipoprotein.

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The ketogenic diet is an effective therapy used in the treatment of medication-resistant epilepsy. The diet is extremely high in fat, low in carbohydrate, and contains adequate protein to allow for growth. The classic ketogenic diet contains approximately 90% calories from fat and the medium-chain triglyceride ketogenic diet contains approximately 70% from fat, of which 30% to 60% is from medium-chain triglyceride oil.

High-fat diets increase atherogenic apoB-containing lipoproteins and decrease the antiatherogenic high-density lipoprotein cholesterol.[1] This raises a concern about the use of prolonged high-fat diet treatments in children. Recent studies[2,3] have shown that nearly half of children treated with the ketogenic diet were able to maintain or gradually metabolize the extra fat they consumed to achieve healthy cholesterol levels.

There have been no reports examining the effects of the ketogenic diet on children with pre-existing hyperlipidemia prior to ketogenic diet initiation. Our aim was to assess the change in lipid levels during the ketogenic diet treatment in children with pre-existing hyperlipidemia.

Materials and Methods

A retrospective chart review of 160 children treated with the medium-chain triglyceride or classic ketogenic diet at the Hospital for Sick Children (SickKids), Toronto, from September 2000 to May 2011 was performed. The study was approved by the SickKids Research Ethics Board.

Lipid profiles were assessed and screened for hyperlipidemia prior to starting the ketogenic diet. Hyperlipidemia was defined as lipid levels above the reference ranges in use at SickKids, which were adapted from Pediatric Reference Intervals.[4] Fasting serum lipid levels, including total cholesterol, low-density lipoprotein, triglycerides, and high-density lipoprotein were collected. Total cholesterol/high-density lipoprotein ratio was calculated. See Table 1 for the laboratory lipid references ranges used in this study. Detailed medical histories were obtained for each child prior to diet initiation, including seizure frequency and family history of hyperlipidemia.

Children with pre-existing hyperlipidemia were prescribed diets containing very low saturated fats (10%-11% of daily calorie intake), and low dietary cholesterol (less than 80 mg/d), with no added trans-fatty acids, while optimizing poly- and monounsaturated fat. Omega-3 supplementation was added if triglyceride levels increased above the

[1] Department of Pediatrics, Division of Neurology, The Hospital for Sick Children, Toronto, Ontario, Canada

Corresponding Author:
Yeou-Mei Christiana Liu, MSc, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada.
Email: christiana.liu@sickkids.ca

Table 1. Lipid Levels Before and During KD Treatment.

	TC (mean ± SD)	LDL (mean ± SD)	HDL (mean ± SD)	TC/HDL (mean ± SD)	TG (mean ± SD)
Reference level, mmol/L (mg/dL)	3.2-4.4 (124-171)	0.98-3.62 (38-140)	0.6-1.81 (23-70)	<4.11	0.4-1.30 (35-115)
Pre-diet (n = 12), mmol/L (mg/dL)	5.49 ± 0.9 (212.4 ± 34.8)	3.34 ± 1.03 (129.3 ± 39.9)	1.5 ± 0.53 (58.1 ± 20.5)	4.11 ± 1.61	1.31 ± 0.63 (116.0 ± 55.8)
3 mo (n = 12), mmol/L (mg/dL)	4.44 ± 0.45 (171.8 ± 17.4) (*P* < .01)	2.29 ± 0.53 (88.6 ± 20.5) (*P* < .01)	1.29 ± 0.54 (49.9 ± 20.9)	4.13 ± 1.70	1.57 ± 0.94 (139.1 ± 83.3)
%Ref[a]	42	83	100	42	42
%Pre-diet[b]	100	80	20	50	50
6 mo (n = 10), mmol/L (mg/dL)	4.34 ± 0.82 (167.9 ± 31.7) (*P* < .05)	2.54 ± 1.0 (98.3 ± 38.7)	1.2 ± 0.51 (46.4 ± 19.7)	4.66 ± 3.4	1.46 ± 0.75 (129.4 ± 66.5)
%Ref[a]	50	60	90	50	40
%Pre-diet[b]	86	71	0	57	83
12 mo (n = 9), mmol/L (mg/dL)	3.73 ± 0.86 (144.4 ± 33.3) (*P* < .01)	1.94 ± 0.71 (75.1 ± 27.5) (*P* < .01)	1.29 ± 0.49 (49.9 ± 19.0)	3.14 ± 1.15 (*P* < .01)	1.11 ± 0.74 (98.3 ± 65.6)
%Ref[a]	78	100	100	89	89
%Pre-diet[b]	100	100	10	78	55

Abbreviations: HDL, high-density lipoprotein; KD, ketogenic diet; SD, standard deviation; TC, total cholesterol; TG, triglycerides.
[a]Percentage of children whose lipid levels were within the reference range.
[b]Percentage of children whose lipid levels improved compared with pre-diet.

reference range and carnitine supplementation was added when carnitine levels were low. For children fed enterally, a low-saturated-fat soy-based protein and safflower oil–based emulsified fat formula was used in order to optimize polyunsaturated fats and decrease saturated fats and trans fatty acids. For children fed orally, the following foods and fats were allowed: corn oil, canola oil, soy oil, sunflower oil, safflower oil, sesame seed oil, extra lean meats, egg whites, and skim dairy products. All fatty meats, egg yolk, cream, butter, lard, animal fat, and palm and coconut oil were excluded from the diet.

The children's lipid profiles were reassessed at 3, 6, and 12 months during ketogenic diet treatment. Percentage of ideal body weight according to height and age was assessed in all children to allow for consistency in statistical analysis. The percentage of ideal body weight was calculated prior to ketogenic diet initiation and at 3, 6, and 12 months after diet initiation to determine the relationship between weight change and lipid levels. Paired *t* tests were performed to compare lipid levels, total cholesterol/high-density lipoprotein, and percentage of ideal body weight of the children treated with the ketogenic diet at diet initiation with levels at 3, 6, and 12 months after diet initiation.

Results

Twelve children (7.4%) with pre-existing hyperlipidemia, aged 0.6 to 8 years (mean ± standard deviation = 3.5 ± 2.9), were identified from 160 children treated with the ketogenic diet for medication-resistant epilepsy. There were 6 boys aged 1 to 8 years (mean ± standard deviation = 3.8 ± 2.7) and 6 girls aged 0.6 to 7.5 years (mean ± standard deviation = 3.2 ± 3.0). Nine children were treated with the classic ketogenic diet (diet ratio ranged from 3:1 to 4:1) and 3 children were treated with the medium-chain triglyceride ketogenic diet (medium-chain triglyceride oil percentage ranged from 40% to 60% of calories). Three- and 6-month follow-up data were available for 12 and 10 children, respectively. Twelve-month follow-up data were available for 9 children.

Mean lipid levels from the 12 children measured prior to diet initiation and at 3, 6, and 12 months of diet treatment are listed in Table 1. Mean total cholesterol level was reduced at all time points and was within the normal reference range by 6 months of diet treatment. Mean triglyceride level also fell within the normal reference range by 12 months, but overall took longer than total and low-density lipoproteins. Mean low-density lipoprotein level reduced at each time point and the mean total cholesterol/high-density lipoprotein ratio fell within the normal reference range by 12 months (Table 1, Figure 1).

Paired *t* tests demonstrated significant reductions in the total cholesterol level at 3 months ($P < .01$), 6 months ($P < .05$), and 12 months ($P < .01$), from pre-diet levels. Significant reductions were also found in low-density lipoprotein levels at 3 months ($P < .01$) and 12 months ($P < .01$) and total cholesterol/high-density lipoprotein after 12 months of diet therapy ($P<.01$). There was no significant change in high-density lipoprotein and triglyceride levels at 3, 6, or 12 months of ketogenic diet therapy (Table 1, Figure 1). There was no significant difference between percentage ideal body weight prior to ketogenic diet initiation when compared to percentage ideal body weight at 3, 6, and 12 months after diet initiation. Ideal body weight percentage values are found in Table 2.

In the cohort of children studied, 9 of the 12 children (75%) were found to have a family history of hyperlipidemia. Despite this reported family history in children with hyperlipidemia prior to diet initiation, there was a significant decrease in total cholesterol, low-density lipoprotein, and total cholesterol/high-density lipoprotein levels during ketogenic diet treatment.

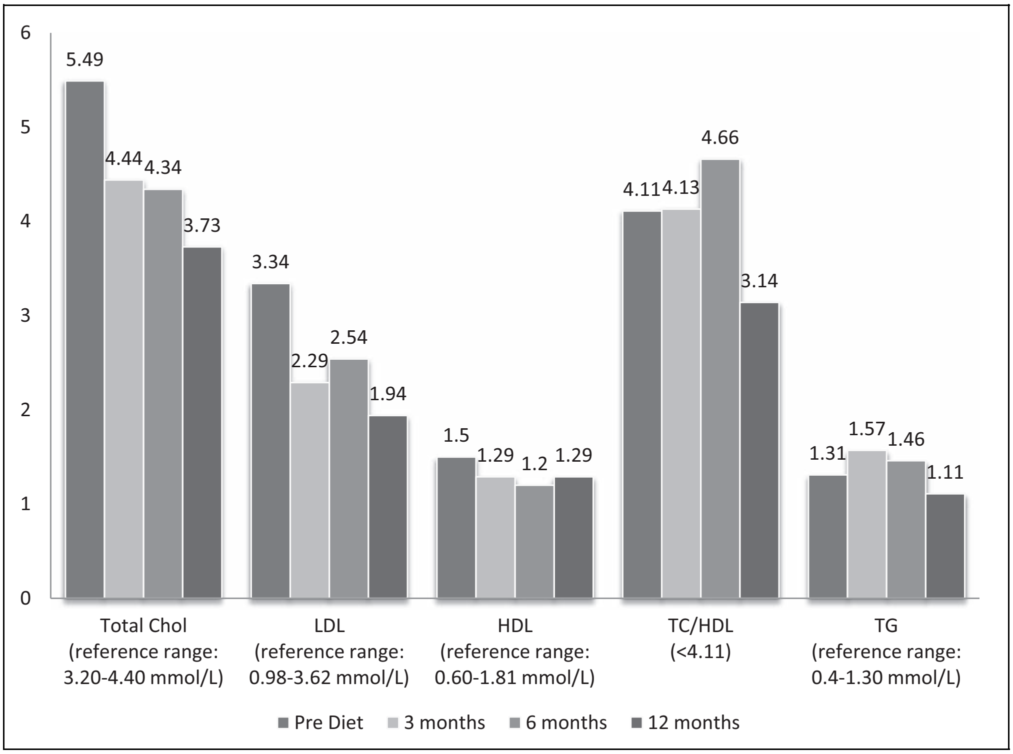

Figure 1. Lipid level pre-diet and at 3, 6, and 12 months on diet.

Table 2. Mean Ideal Body Weight Before and During KD Treatment.

Time point of KD treatment	Mean ideal body weight percentile ± SD
Pre-diet, n = 12	100.8 ± 15.7
3 mo, n = 12	107.3 ± 16.5 (P = .328, NS)
6 mo, n = 10	105.6 ± 11.2 (P = .403, NS)
12 mo, n = 9	97.9 ± 8.7 (P = .628, NS)

Abbreviations: KD, ketogenic diet; NS, nonsignificant; SD, standard deviation.

Discussion

This study was designed to evaluate whether hyperlipidemia can be safely controlled when consuming a high-fat diet (>70% fat). We have demonstrated that despite the high dietary fat content, lipid levels can be controlled in children with hyperlipidemia prior to starting the ketogenic diet. This also highlights the importance of utilizing low-saturated fats when trying to control hyperlipidemia in children with prior elevated lipids. Second, it supports recent studies that children can achieve healthy lipid levels while on a ketogenic diet.[2,3]

The classic ketogenic diet consists of 90% of calories from fat and limits the intake of carbohydrates and protein. The medium-chain triglyceride ketogenic diet consists of approximately 70% of energy derived from fat. The average healthy diet is composed of less than 30% of calories derived from fat; thus, both forms of ketogenic diet contain greater than 2 to 3 times the recommended daily fat consumption for general health. High-fat diets increase atherogenic apoB-containing lipoproteins and cause a decrease in the antiatherogenic high-density lipoprotein.[1] Children treated with high-fat ketogenic diet for medically intractable epilepsy could experience a gradual increase in their lipid levels. There is an added concern about exposing children with pre-existing hyperlipidemia to this extremely high-fat treatment. Most ketogenic diet treatment centers debate the use of ketogenic diet in children with pre-existing hyperlipidemia.

During routine questioning in our pre-diet assessment clinic, all families were asked if there was a family history of elevated cholesterol. No further follow-up with families was completed. Parental reports indicated hyperlipidemia was found primarily among patients' grandfathers and grandmothers with 1 father and 1 uncle. We identified 12 children (7.4%) with hyperlipidemia among a cohort of 160 children aged 0.6 to 16.2 years, with medically intractable epilepsy.

Eight of these 12 children were under 6 years of age. Lipid levels in childhood are known to be familial[5]; however, screening for familial hyperlipidemia only identifies a small percentage of high-risk youth.[6] The Canadian Health Measures Survey (2007-2009) conducted by Statistics Canada[7] identified rates of dyslipidemia in children between the ages of 6 and 19 years. Less than 32% of children had elevated total cholesterol levels, 7% with elevated low-density lipoprotein, 9% with elevated triglyceride, and 12% with abnormal total cholesterol/high-density lipoprotein.[7] No survey data for children under 6 years of age was obtained.

Although data are limited in young children, the rate of hyperlipidemia in our cohort is in keeping with that of the Canadian pediatric population.

Table 3. Recommended KD Fat Intake for Children With Hyperlipidemia.

	Saturated fat	Poly- and mono-unsaturated Fat	Cholesterol	Added trans fat	Cholesterol + protein
Classic KD	10%-11% daily calorie intake	78%-80% daily calorie intake	<200 mg/d	0 mg/d	10%-13% daily calorie intake
MCT KD	6%-10% daily non-MCT calorie intake	34%-52% daily non-MCT calorie intake	<200 mg/d	0 mg/d	29% daily calorie intake

Abbreviations: KD, ketogenic diet; MCT, medium-chain triglyceride; SD, standard deviation.

Table 4. Recommended Foods for Children With Preexisting Hyperlipidemia Treated With KD.

Food groups	Suggested	Not suggested
Lean meats/skinless poultry/ egg whites	Skinless chicken breast, turkey breast; lean beef, lean pork, fish, egg white, lean wild game, fatty fish	Bacon, chicken or turkey skin, egg yolks, all fatty meats
Poly- and/or mono-unsaturated vegetable oil	Canola oil, olive oil, sunflower oil, safflower oil, corn oil, soybean oil, sesame seed oil, walnut oil, MCT oil	Butter, lard, palm oil, coconut oil
Skim milk–based dairy products	Skim milk, nonfat yogurt	Whole, 2%, or 1% milk and products, whipping cream

Abbreviations: KD, ketogenic diet; MCT, medium-chain triglyceride.

In this cohort, we tailored the fat intake of children with pre-existing hyperlipidemia prior to starting the ketogenic diet by optimizing polyunsaturated and monounsaturated fats intake and limiting saturated fat, dietary cholesterol, and trans fatty acids. Details are found in Table 3. The amounts of poly- and mono-unsaturated fats used were at the discretion of parents for children who were fed orally but not for those who were fed enterally. We used omega-3 fatty acid supplementation of 1500 to 2500 mg of docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) per day following Health Canada's recommendation[8] if triglyceride levels were elevated.[9,10] Carnitine supplementation was used to maintain carnitine levels necessary for balancing lipid levels when carnitine levels were low.[11] For children who received formula-based ketogenic diet, a soy-based protein and safflower oil–based emulsified fat formula was used. It optimized the intake of polyunsaturated fats and decreased the intake of saturated and trans fatty acids. The commercially available liquid KetoCal (Nutricia North America) contains lower saturated fat and cholesterol than the powder formulation that can also be used. Food choices for children who consumed an oral classic or medium-chain triglyceride ketogenic diet are listed in Table 4.

Physical activity and optimizing the intake of polyunsaturated and monounsaturated fats while decreasing the consumption of saturated fat, trans fatty acids, and dietary cholesterol are recommended for managing hypercholesterolemia in children.[5,12-15] The American Heart Association and the National Cholesterol Education Program recommend maintaining a desirable body weight.[13] Ten of 12 of the children in our study cohort engaged in only limited physical activity because of their neurologic disability. Given the exercise limitations of these children, it is most likely that diet management was the primary factor in the reduction of lipid levels.

A single study examined the long-term effects of the ketogenic diet when used to reduce body weight in obese patients. These patients had a significant decrease in their total cholesterol, low-density lipoprotein, and triglyceride levels, whereas high-density lipoprotein increased significantly.[16] The children in our study had no statistically significant change in weight over the year they were treated with the ketogenic diet. Weight loss did not appear to be the factor that contributed to the lower lipid levels found in our ketogenic diet population.

All of the children in this cohort maintained a healthy weight. Healthy body weight was defined as 90% to 110% ideal body weight.[17] The United States Centers for Disease Control and Prevention (CDC) recommends the use of body mass index to screen for obesity in children beginning at 2 years old.[18] We were not able to use body mass index to measure the growth in 7 children in the cohort as they were under the age of 2 years. Percentage of ideal body weight was considered an acceptable surrogate marker by our group to screen for a healthy weight.

The findings from our study suggest that those children with hyperlipidemia and medication-resistant epilepsy can benefit from a ketogenic diet therapy without the risk of a worsening of their lipid status. This study demonstrates that total and low-density lipoprotein cholesterol levels can be reduced to within the normal reference range despite treatment with the high-fat ketogenic diet for 1 year. The children in our cohort also had a decrease in the total cholesterol/high-density lipoprotein ratio with no significant decrease in high-density lipoprotein levels.

The small sample size of our cohort does not permit a statistical comparison of lipid levels in children treated with the classic and the medium-chain triglyceride ketogenic diets. However, review of the data do not identify any clear differences in lipid levels of children treated with these different ketogenic diet formulations.

Increased consumption of polyunsaturated and monounsaturated fats including omega-3 fatty acids, while decreasing the intake of trans fat, saturated fat, and cholesterol, was the most likely factor that led to normalization of lipid levels in children with pre-existing hyperlipidemia. With careful monitoring of lipid levels, and consumption of healthy fats, there is no need to restrict children with hyperlipidemia from starting the ketogenic diet. Concern for heart health has limited treatment options for patients, especially for adults, with medication-resistant epilepsy. If lipid levels can be controlled on a high-fat diet, it can remove barriers to starting ketogenic therapy for adults and achieving improved seizure control.

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Authors Contributions

YMCL was the principal research investigator and wrote the first draft of the manuscript. HL assisted with statistical analysis. EJD, director of the ketogenic diet program, was the senior author and, along with YMCL, HL, and MMZ, undertook major revisions of the manuscript. All authors were responsible for care of the patients and took part in revising the manuscript.

Ethical Approval

Approved by the Research Ethics Board (# 0019980037), Research Institute at the Hospital for Sick Children, Toronto, Ontario, Canada.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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