Management and Risk Factors for Dyslipidemia with the Ketogenic Diet

Junaid Nizamuddin, BS
Junior Medical Student

Zahava Turner, RD
Registered Dietitian

James E. Rubenstein, MD
Assistant Professor, Pediatrics and Neurology

Paula L. Pyzik, BA
Research Coordinator

Eric H. Kossoff, MD†
Assistant Professor, Pediatrics and Neurology

1 The Johns Hopkins University School of Medicine
2 The John M. Freeman Pediatric Epilepsy Center, Departments of Neurology and Pediatrics, The Johns Hopkins Medical Institutions, Baltimore, Maryland 21287 USA

†Author for Correspondence:
Eric H. Kossoff, MD
Suite 2158 - 200 North Wolfe Street
The Johns Hopkins Hospital
Baltimore, MD 21287
Phone: (410) 614-6054
Fax: (410) 614-2297
Email: ekossoff@jhmi.edu

Word Count: 2,099
Tables: 4
ABSTRACT

A prospective study was performed of all children started on the ketogenic diet at our institution for intractable epilepsy from January 2003 to March 2007 (n=137), examining for baseline and follow-up total cholesterol and triglyceride levels. Interventions for dyslipidemia were analyzed for their effectiveness. At baseline, 25% of children had hypercholesterolemia (>200 mg/dl), which increased to 60% for those receiving the ketogenic. Children receiving a solely formula-based ketogenic diet were less likely to have hypercholesterolemia than those eating solid food after adjusting for age and initial ketogenic ratio ($P<0.001$). Only a slightly higher likelihood of a 20% decrease in cholesterol occurred for those children in whom a dietary intervention was made compared to observation alone (60% vs. 41%), $P=0.11$. Hypercholesterolemia occurs in most children receiving a solid food based ketogenic diet but improved in approximately half, even without interventions.

Key Words

Ketogenic, diet, cholesterol, lipids, management, children
The ketogenic diet is a high fat and low carbohydrate diet that has been demonstrated as effective for intractable epilepsy in children.\textsuperscript{1,2} The ketogenic diet is typically started using a 4:1 ketogenic ratio (fat: carbohydrate and protein combined), although a 3:1 ratio diet is also widely used, particularly for infants and adolescents to maximize protein and carbohydrates, respectively.\textsuperscript{1} Because fats contain more than twice as many calories per gram than protein or carbohydrate, the fat content of the classic 4:1 diet represents 90\% of the child’s total calorie intake. The Modified Atkins diet is a 1:1 ketogenic ratio, but still provides the majority (60\%) of calories as fat.\textsuperscript{3}

Previous studies have shown that the ketogenic diet causes an increase in both total cholesterol and triglycerides by 30\%, and while receiving the ketogenic diet 60-85\% of children will have abnormal lipid results at least temporarily.\textsuperscript{4-6} While it has not been established whether typically short-term use of the ketogenic diet in childhood leads to a later increased risk of atherosclerosis in adulthood\textsuperscript{4}, the periodic serum monitoring of lipid profiles occasionally leads the neurologist, dietitian, and parents to have concerns when abnormalities are identified.

Several potential interventions have been reported as effective in small studies for dyslipidemia on the ketogenic diet, including carnitine supplementation, substitution of polyunsaturated fats or medium-length chain triglycerides for saturated fats, and reducing the ketogenic ratio. Carnitine supplementation was reported to reduce triglyceride levels in three children, although this was seen only after the dose was significantly increased in two.\textsuperscript{7} Another study found that the addition of polyunsaturated fats to the ketogenic diet decreased the cholesterol levels in three patients.\textsuperscript{8} In addition, the use of medium chain triglycerides does appear to produce less of a dyslipidemia than the classic diet.\textsuperscript{9} Although
lower ketogenic ratios would be theoretically beneficial due to lower fat content, a prospective randomized study found no difference in lipid values between 3:1 and 4:1 ketogenic ratios.\textsuperscript{10} We hypothesized that dyslipidemia continues to be high in children receiving the ketogenic diet, but the previously mentioned interventions would be successful in reducing laboratory abnormalities when implemented.

**Methods**

This study included all children started on the ketogenic diet at the Johns Hopkins Hospital, Baltimore, Maryland between January 2003 and March 2007. Children were fasted for 24 to 48 hours before being gradually started on increasing calories of either a 3:1 or 4:1 ratio diet.\textsuperscript{1} Children were evaluated in clinic every 3-4 months for the first year, and then every 6 months thereafter to monitor seizure control, medications, nutritional status, and laboratory values. Lipid values (fasting), including total cholesterol, triglyceride, HDL (high density lipoprotein) and LDL (low density lipoprotein), were ordered at baseline and prior to every follow-up visit, with more frequent results requested for children with subsequently identified dyslipidemia. The longest date of follow-up on the KD was 4 years in this cohort. Family history of dyslipidemia was not routinely obtained.

Dyslipidemia was defined as total cholesterol >200 mg/dl, triglyceride >130 mg/dl, low density lipoprotein >130 mg/dl, and high density lipoprotein <35 mg/dl at any available time point. The value used was the highest available for each individual child. Cholesterol changes were examined for all children with total cholesterol >200 mg/dl, with an improvement in total cholesterol levels defined for this study as > 20% reduction in the
level at the next time point for evaluation, typically 3-6 months later. Children for whom potential lipid level-lowering interventions were made were compared to the other patients with cholesterol levels >200 mg/dl in whom observation alone was employed in order to determine the effectiveness of potential interventions overall. Patients in whom two sequential interventions were made were counted only once for this particular analysis. Also, potential loss of seizure control on the ketogenic diet was evaluated after interventions were made, although ketogenic ratio reduction has been demonstrated not to be problematic after 3 months on the diet.¹⁰

Children receiving the ketogenic diet had informed consent obtained prior to starting, which was approved by The Johns Hopkins Committee on Clinical Investigation. Categorical data were analyzed using the Fisher exact test for independence of rows and columns. Numerical data were analyzed using the Wilcoxon rank-sum test. Multiple logistic regression was then used to examine the relationship between cholesterol and select covariables. The significance level for all tests was \( P=0.05 \).

**Results**

**Overall lipid changes**

Over the study period, 137 children with intractable epilepsy were started on the ketogenic diet. Baseline lipid values were available for 121 of these children, of which 99 had follow-up results. At initiation of diet, 30 children (25%) had total cholesterol >200 mg/dl, and one (1%) had total cholesterol level >300 mg/dl (Table 1). This was nearly identical to our previously reported prevalence prior to 2003, in which 22% had total cholesterol >200 mg/dl at baseline before starting the ketogenic diet.⁴ The median baseline
total cholesterol was 167 mg/dl (range: 98-316 mg/dl) and triglyceride was 80 mg/dl (range: 27-690 mg/dl).

At follow-up time periods, 59 (60%) had total cholesterol >200 mg/dl, and 20 (20%) had cholesterol >300 mg/dl. Again, this was very similar to our previously reported prevalence, in which 61% had total cholesterol >200 mg/dl at follow-up. The median total cholesterol values on the ketogenic diet was 204 mg/dl (range: 42-549 mg/dl) and triglyceride was 109 mg/dl (range: 25-3580 mg/dl).

**Predisposing factors for dyslipidemia**

Children with hypercholesterolemia at follow-up were compared to the minority (40%) who had normal total cholesterol values while receiving the ketogenic diet (Table 2). When analyzed independently, both younger age and use of a formula-only ketogenic diet were less likely to result in a total cholesterol >200 mg/dl, whereas male gender and 3:1 ratio only trended towards statistical significance. Multivariate analysis was then performed to identify and account for potential covariates (e.g. younger age children being more likely to be formula-fed). In a multiple logistic regression, children receiving only a formula-based ketogenic diet were less likely to have a cholesterol >200 mg/dl (Odds ratio = 2.85, 95% confidence interval: 1.67 to 4.04, \( P<0.001 \)) or >300 mg/dl (Odds ratio = 1.58, 95% confidence interval: 0.18 to 2.89, \( P=0.03 \)) than children who ate solid foods. Neither age nor ketogenic ratio was found to have a significant association with cholesterol >200 or 300 mg/dl after adjusting for formula as the sole dietary intake.

**Effects of dietary and supplementary interventions**
Children with hypercholesterolemia on the ketogenic diet were then evaluated for the impact of dietary manipulations that were made in order to reduce total cholesterol. Interventions were made in 7 of 39 (20%) of the children with cholesterol 200-299 mg/dl and in 8 of 20 (40%) with cholesterol >300 mg/dl. The median duration receiving the ketogenic diet when interventions were made was 9 months (range: 3-36 months). No patient had more than one intervention made at any single time point.

Of the 15 patients for whom interventions were made, 9 (60%) had at least a 20% decrease in total cholesterol when rechecked several months later. Five (33%) improved to a normal total cholesterol value (<200 mg/dl). Table 3 lists the interventions made for children who showed improvement in cholesterol levels and those that did not. No single intervention appeared most likely to reduce total cholesterol.

Three children had two consecutive interventions made, typically after the first intervention was not perceived to be adequate. Only one had resultant improvement after a second intervention, and she had total cholesterol of 298 mg/dl and triglycerides of 3580 mg/dl after 9 months on the ketogenic diet. A reduction in her ketogenic ratio from 3:1 to 2.5:1 led to a slight reduction, and the subsequent addition of medium chain triglycerides improved her total cholesterol to 236 mg/dl and triglycerides to 118 mg/dL.

Among the 44 children with cholesterol >200 mg/dl for whom no dietary interventions were made (observation only), 7 did not have available follow-up lab results. Of the remaining 37 children, 15 (41%) had a reduction in total cholesterol when retested after at least 3 months, despite no interventions. There was a slightly increased likelihood of improvement following an intervention when compared to observation alone, 60% vs. 41%, $P=0.11$. Seven (19%) improved to a normal total cholesterol (<200 mg/dl) without
intervention, which also only trended towards fewer children when compared to when an intervention was made (33%), \( P = 0.22 \).

Only one child had increased seizures after an intervention, which was a gradual decrease in the ketogenic ratio from 4:1 to 2:1 after 4 years on the diet due to total cholesterol of 362 mg/dl. Although her cholesterol improved to 176 mg/dl, her seizures worsened and the ketogenic ratio was increased to 3:1 without a resultant elevation in her total cholesterol. No child in this study discontinued the ketogenic diet specifically as a result of dyslipidemia.

Discussion

This study showed that dyslipidemia remains a common adverse effect of the ketogenic diet. Although the majority of children that were treated with the four potential dietary and supplement interventions had a reduction in their total cholesterol values, nearly half who were solely observed over time also did. This latter finding was surprising as well as reassuring and suggests that children receiving the ketogenic diet can metabolize the higher fat and cholesterol provided by the ketogenic diet over time. This confirms results in children who have been continuously treated with the ketogenic diet for over 6 years.\(^1\)

Perhaps most interestingly, there was a highly significant association between a formula-only ketogenic diet and normal total cholesterol values. An analysis of sample ketogenic diet menus revealed that about 60% of the fat in solid-food ketogenic diets is saturated fat, compared to approximately 20% saturated fat in the two primary ketogenic diet formulas (Table 4). Although the dietary interventions to increase polyunsaturated
fats and medium chain triglycerides should reduce the amount of saturated fat eaten, one suspects it would not approach the low percentage provided by ketogenic diet formulas. This difference between the two ketogenic diet types may be the basis of another potential dietary intervention: switching children exhibiting dyslipidemia to a solely formula-based diet. This would be relatively straightforward in a child receiving the ketogenic diet as a combination of solid and formula ketogenic diet, but might be overly restrictive for a solely solid food-fed child.

There were several limitations to this study. Instituting the dietary interventions required cooperation from parents, and the degree to which the changes were made likely varied from prescribed to some degree. Although fasting laboratory values were requested, it is possible that some parents did not rigorously enforce this before venipuncture. In addition, many of the children who exhibited improved total cholesterol levels without having interventions made could have actually had some minor, but significant, dietary changes made as a result of parents choosing ketogenic diet recipes with less butter or animal fats on their own. Lastly, not all interventions made were followed universally with regular laboratory monitoring in this cohort, including ketogenic diet discontinuation.

Given the high incidence of dyslipidemia and only modestly higher success of interventions made compared to observation alone, we believe that there is a need for improved treatment strategies. One possible option may be to implement multiple interventions at the same time. Since only one patient in this study who had a dietary change made had a possible worsening of seizure control, the benefits of these dietary interventions appear to outweigh any potential risks. In addition, it may be advantageous to start all children at ketogenic diet onset with increased proportions of polyunsaturated
fatty acids\textsuperscript{12} or medium chain triglycerides, especially those with a family history of dyslipidemia. Although starting children on lower ketogenic ratios has been advocated specifically for potential cardiovascular benefits, the Modified Atkins diet (a 1:1 ketogenic ratio) still increases total cholesterol in both children and adults, and a 3:1 ratio at ketogenic diet onset may be less beneficial for seizure control.\textsuperscript{3,10,13}

Ultimately, however, there is no evidence at this time that having temporarily elevated total cholesterol levels while on the ketogenic diet will cause patients to develop early atherosclerosis or a higher risk of cardiovascular disease, so it remains unclear exactly how important it is to make dietary interventions in order to better control serum lipid levels.\textsuperscript{4} Further studies to evaluate the long-term risk of these elevations in lipid profiles in both children actively receiving the ketogenic diet and those who discontinued it years prior are necessary.

**Acknowledgements:** Supported in part at the Johns Hopkins Hospital by the Pediatric Clinical Research Unit, NIH/National Center for Research Resources grant M01-RR00052. Mr. Nizamuddin was supported by the Johns Hopkins Summer Medical Student Training Program. The authors are grateful for the statistical assistance of Dr. Rana Hamdy.
References


8. Cutler LJ, Chee CM, Bergqvist CAG. Manipulation of the ratio of saturated to unsaturated fat can successfully lower the cholesterol while maintaining the efficacy of the ketogenic diet (abstract). *Epilepsia* 2005;46:S227-S228.


Table 1. Dyslipidemia in children at baseline and on the ketogenic diet over the study period. Absolute numbers expressed with percentiles in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Highest Follow-Up Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol &gt;200 mg/dl</td>
<td>(30/121) 25%</td>
<td>(59/99) 60%</td>
</tr>
<tr>
<td>Cholesterol &gt;300 mg/dl</td>
<td>(1/121) 0.8%</td>
<td>(20/99) 20%</td>
</tr>
<tr>
<td>Triglycerides &gt;130 mg/dl</td>
<td>(22/119) 18%</td>
<td>(49/96) 51%</td>
</tr>
<tr>
<td>Triglycerides &gt;200 mg/dl</td>
<td>(6/119) 5%</td>
<td>(25/96) 26%</td>
</tr>
<tr>
<td>LDL* &gt;130 mg/dl</td>
<td>(21/110) 19%</td>
<td>(48/93) 52%</td>
</tr>
<tr>
<td>HDL** &lt;35 mg/dl</td>
<td>(8/114) 7%</td>
<td>(23/95) 24%</td>
</tr>
</tbody>
</table>

*=low density lipoprotein; **=high density lipoprotein.
**Table 2.** Cholesterol levels of children receiving the ketogenic diet with follow-up lab results (n=99). Medians expressed with range in parentheses, absolute numbers expressed with percentiles in parentheses.

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol &lt; 200 mg/dl (n = 40)</th>
<th>Cholesterol &gt; 200 mg/dl (n = 59)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>1.5 (0.4-14.8)</td>
<td>4.0 (0.3-10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median number of prior anticonvulsants</td>
<td>5 (0-9)</td>
<td>5 (1-20)</td>
<td>0.85</td>
</tr>
<tr>
<td>Median initial seizure frequency per month</td>
<td>200 (4-12000)</td>
<td>300 (1-7500)</td>
<td>0.47</td>
</tr>
<tr>
<td>Caucasian race</td>
<td>32 (80%)</td>
<td>48 (81%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Female gender</td>
<td>18 (45%)</td>
<td>36 (61%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Initial 4:1 ketogenic ratio</td>
<td>21 (53%)</td>
<td>34 (58%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Formula-only ketogenic diet</td>
<td>31(78%)</td>
<td>10 (17%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Greater than 90% improvement at 3 months</td>
<td>16 (40%)</td>
<td>30 (59%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Greater than 90% improvement at 6 months</td>
<td>16 (40%)</td>
<td>27 (46%)</td>
<td>0.36</td>
</tr>
</tbody>
</table>
Table 3. Dietary interventions made in ketogenic diet patients with hypercholesterolemia (n=15) and resultant likelihood of improvement ($\geq 20\%$ reduction in total cholesterol).

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Improvement</th>
<th>No Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medium Chain Triglyceride Oil</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Substitution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyunsaturated Fat Substitution</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Decreasing Ratio</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Carnitine Addition</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
**Table 4.** Average cholesterol and fat content in one day using three different ketogenic diets (4:1 ratio and 1000 calories).

<table>
<thead>
<tr>
<th></th>
<th>Solid food diet*</th>
<th>Modular formula**</th>
<th>Nutricia KetoCal™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (milligrams)</td>
<td>454</td>
<td>0***</td>
<td>0***</td>
</tr>
<tr>
<td>Total Fat (grams)</td>
<td>104</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Saturated Fat (grams)</td>
<td>63</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Saturated Fat as Percent of Total Daily fat</td>
<td>60%</td>
<td>20%</td>
<td>23%</td>
</tr>
</tbody>
</table>

*This represents using three distinct meals to create a 1000 calorie diet, including chicken, salmon, eggs, oil, heavy whipping cream, and vegetables.

** Novartis Microlipid™, Ross Carbohydrate Free™, and Ross Polycose™ in combination to create a 4:1 ratio.

***0.01 mg of cholesterol for both products.