Introduction:

The ketogenic diet is an attractive alternative treatment for pediatric epilepsy and when medications have failed (1). A meta-analysis showed a pooled odds ratio of 2.25 (95% confidence interval = 1.69-2.98) for greater than 50% seizure reduction in patients staying on a ketogenic diet vs. discontinuing the diet (1). The ketogenic diet to treat pediatric epilepsy is composed of low carbohydrate intake, low protein intake, and unrestricted fat intake. Calories are not restricted and the maintenance of optimal weight is not a goal of this treatment. The diet is generally adhered to for three months as a trial period. If successful, the diet is continued as long as the treatment remains effective (1, 7). The purpose of the diet is to produce ketosis in the body, a state in which the body and the brain use ketone bodies as their source of energy instead of glucose (7). However, the high fat content of the diet is a concern in a general sense, as lipid levels could increase leading to higher risk for cardiovascular disease (8). The purpose of this review is to review lipid levels in pediatric epileptic patients to see if increased lipid levels were a consequence of undertaking a ketogenic diet.

Methods:

Literature Search

PubMed was searched with the terms “Atkins,” “epilepsy,” “ketogenic,” “pediatric,” “lipid,” and “cholesterol.” To keep findings current, the literature search was limited to the year 2000 to the present for the article publication date. Other limits included links to full text, studies performed in humans, and in the English language. The types of studies included were clinical trials, meta-analyses, and randomized control trials.

Article Selection

Upon searching PubMed, it was seen that very few articles measured lipid levels in children with epilepsy treated with a ketogenic diet. Therefore, any article that included some measure of lipid levels was included in the review.

Quality Assessment

The six articles that met the criteria included two articles that reported only “increased serum cholesterol or triglycerides” (1) or “increased serum lipid levels” (2) as a side effect without actual numerical measurements reported. Also, there was only one randomized control trial (6) which did not examine the effects of treatment with the diet vs. no treatments, but instead compared the effects of different initial carbohydrate intake (10g/day vs. 20 g/day). The rest of the articles were either prospective studies or reviews of other studies done which were also not randomized controlled trials (1, 2, 3, 4, 5, 6). Also, two of the trials had very small sample sizes (3, 4) which made the results not as reliable. While the efficacy of the diet has been well studied, more work needs to be done to assess increases in lipid levels in children on the ketogenic diet.

Results

The results found from the six articles are summarized in Table 1. One meta-analysis that evaluated the most common side effects for children on the ketogenic diet for three months or more found four percent of the 1,084 patients studied to have “increased serum cholesterol or triglycerides” (1). No data was reported as to the average increase or the values that determined when increased serum cholesterol or triglycerides were considered a negative side effect.

Similarly, another systematic review of several articles found that 28 of the 1,066 patients from the studies had “increased serum lipid levels” (2). This was 2.63% of the total patient population and was the second most common side effect of the diet besides vomiting (2).

One prospective study did measure and report numerical values for lipid levels before and after treatment with a ketogenic diet. Total cholesterol increased from 192 mg/dL to 221 mg/dL, an increase with a p-value of <.05 (3). HDL and LDL cholesterol both increased, with LDL increasing more than HDL. Triglycerides also increased, although none of those increases (HDL, LDL, or triglycerides) were statistically significant (3). One important consideration in evaluating this data, however, is that only twenty patients were evaluated in this study. The small population did produce statistically significant results, but the results should be viewed with the small sample in mind.

Another study by the same primary researcher attempted to find the ideal starting carbohydrate limit for seizure reduction in pediatric patients with epilepsy (6). The experiment was randomized in that patients were randomly assigned to receive either 15 grams of carbohydrates per day or 20 grams of carbohydrates per day when beginning the ketogenic diet (6). Again, total cholesterol increased significantly from 165 mg/dL to 238 mg/dL (p-value <.02) (6). LDL cholesterol increased from 95 mg/dL to 161 mg/dL with a p-value of .03. Triglycerides also increased from 70 mg/dL to 115 mg/dL with a p-value of <.10 (6). The effects on lipid levels in this study were definitely dramatic and show the importance of monitoring lipid levels when placing children on a ketogenic diet.

However, we also need to be careful when interpreting these data. These data are taken from a sample size of only thirteen. Eight of these patients had their final lipid levels taken six months after beginning the ketogenic diet; for five of the patients, lipid levels were obtained at three months (6). The small sample size and the discrepancy of when the final values were taken should definitely be considered when evaluating these data.

Another prospective trial was performed on fourteen pediatric subjects with epilepsy who had not responded to any medications (4). The study reports that “two patients (patients 2 and 10) showed hyperlipidemia respectively with 379 mg/dL of cholesterol and 475 mg/dL of triglyceride within the first month, but it was transient” (4). No comment is made on when these issues resolved or what the later values were that made them not considered “hyperlipidemia.” Again, we must be cautious in interpreting these data since the sample size was so small. Also, patient two with the high cholesterol level had several complications besides hyperlipidemia and stopped the treatment (4). This patient’s results, then, should be considered with these complications in mind.

There was one study considered in this review that focused directly on the ketogenic diet’s effects on lipid levels. This was a prospective study performed for six months on 141 patients (5). Lipid levels measured included apolipoprotien B (apoB)-containing lipoprotiens (LDL and very low density lipoprotein (VLDL)) and HDL (the major apoliporotein A (apoA-I)-containing lipoprotein) (5). The table below gives a summary of the results. Of particular interest to this review are the increases in total cholesterol from 174 mg/dL to 232 mg/dL with an adjusted mean difference of 58 mg/dL; the LDL cholesterol increase from 99 mg/dL to 148 mg/dL with an adjusted mean difference of 50 mg/dL; the triglycerides increase from 96 to 154 mg/dL with an adjusted mean difference of 58 mg/dL; and the HDL cholesterol decrease from 56 mg/dL to 49 mg/dL with an adjusted mean difference of -7 mg/dL (5). The p-value on all of these changes was less than .001 (5).

This study shows that it is very important to consider lipid levels in pediatric patients receiving a ketogenic diet. The results of this study were the most valuable of this review because of the large sample size and the specific focus on lipid levels for the measurements.

Discussion

The effect of a ketogenic diet to treat pediatric epilepsy has been extensively studied. However, most studies evaluating this treatment focus on the effectiveness of seizure reduction with less consideration on the potential effects on the children's lipid levels.

From the studies considered in this review, it is clear that increased lipid levels are a side effect that should be taken under consideration when prescribing the ketogenic diet for pediatric epilepsy. All of the studies which reported lipid levels showed total cholesterol and triglycerides to be increased. Average total cholesterol was increased to 221 mg/dL at a minimum (3), with a 238 mg/dL average being reported by two of the studies (5, 6). According to the American Heart Association (AHA), a total cholesterol of 200-239 mg/dL is considered borderline-high risk and a level of 240 mg/dL or above is considered high risk (7). At the borderline-high risk level, the AHA explains that a total increase in cholesterol could be due to a normal LDL level and a high HDL level, but this is not the case in our patients (5). When total cholesterol reaches 240 mg/dL or above, patients are at twice the risk of coronary heart disease as patients with a cholesterol level of 200 mg/dL (7).

The increase in LDL cholesterol is a particularly concerning finding. The average of 148 mg/dL for LDL cholesterol (5) again puts patients in the "borderline high" risk range for heart attack and stroke (7). The average triglyceride level of 154 mg/dL (5) again put our patients in the borderline-high category, and is one of the risk factors for metabolic syndrome (7). Metabolic syndrome increases the risk for diabetes, heart disease, and other disorders (7).

An important consideration for doctors administering a ketogenic diet to pediatric patients with epilepsy is the average increase in total and LDL cholesterol, as well as triglycerides. The average increase for each of these is 58, 50, and 58 mg/dL, respectively (5). Physicians should be sure to consider this when treating patients whose lipid levels are already high as this increase could prove dangerous to the patient.

Of course, the main consideration of whether to administer the ketogenic diet is the patient's quality of life. The ketogenic diet has been shown to be effective in reducing seizures. Certainly a child and his or her family enjoy a better quality of life when seizure reduction is reduced by 50% or more. The risk factors associated with increased lipid levels may not be as important to the patient, the family, or the physician as finding a therapy to reduce seizure frequency. More study needs to be done on the long term effects of increased lipid levels in children treated with the ketogenic diet so that physicians can know the risks associated with the diet (9).

Conclusions

The ketogenic diet when being used to treat pediatric epilepsy is a good choice when other therapies have failed. It shows a relatively good response in reducing seizure frequency (1, 2, 3, 4, 6) and thereby improves the patient's quality of life.

However, physicians should be aware that use of this type of therapy has resulted in increased lipid levels. Of particular concern are increases in atherogenic apolipoprotien B-containing compounds (LDL, VLDL, triglycerides) which were shown to increase significantly in several studies (2, 3, 5, 6). More study is needed to determine the duration of these changes and the long term effects on risk of cardiovascular and metabolic disease resulting from the ketogenic diet and increased lipid levels.

Table 1. Summary of Clinical Trials Testing Ketogenic Diets in Epileptic Children

Primary Author	Year	Study Design	n	Main measure of effect	Results of main measure	Effects on lipid levels (numbers in mg/dL)
Henderson, CB	2006	Meta-analysis	1084	Seizure reduction, success defined as greater than 50% seizure reduction	Odds ratio of greater than 50% reduction in seizures for adherers to the diet was 2.24	4% of patients had increased serum cholesterol or triglycerides
Keene, DL	2006	Systematic review	972, 1066*	Seizure reduction	At 6 months of diet, an average of 15.6% of the patients seizure-free, while 33.0% reported greater than 50% reduction in seizure frequency	28 of 1066 patients (2.63%) had increased serum lipid levels. Most common side effect after vomiting.
Kossoff, EH	2006	Prospective study	20	Seizure reduction after six months	10 (56%) of 18 had improved seizure control, and four (22%) of 18 maintained the seizure reduction noted after 1 month	Average total cholesterol increased from 196 to 221, LDL cholesterol increased from 108 to 130
Kang, HC	2007	Prospective study	14	Seizure reduction and diet tolerance	Five (36%) had >50% seizure reduction, and three (21%) were seizure free. Diet tolerated by 12 (86%)	Two patients (14%) showed hyperlipidemia respectively with 379 of cholesterol and 475 of triglyceride
Kwiterovich, PO	2003	Prospective study	141	Effects of ketogenic diet on lipid levels	See next column and table 2	Average total cholesterol increased from 174 to 232, LDL

						from 99 to 148, triglycerides 96 to 154
Kossoff, EH	2007	Randomized comparison trial	20	Seizure reduction	Significantly higher likelihood of >50% seizure reduction at 3 months for children started on 10 g carbohydrate per day. No difference in efficacy between the initial carbohydrate limits after 1 or 6 months	Average total cholesterol 165 to 238, LDL 95 to 161, triglycerides 70 to 115

* 972 for efficacy, 1066 for side effects

Table 2. Mean Plasma Levels of Lipids, Lipoproteins, and Apolipoproteins at Baseline and 6 Months in Patients Receiving the Ketogenic Diet

Plasma Level	Baseline, Mean (SD), mg/dL	6 Months, Mean (SD), mg/dL	Adjusted Mean Difference (95% CI), mg/dL*	*t*†	*df*	*P* Value
Total cholesterol	174 (46)	232 (94)	58 (44-72)	7.8	236	<.001
LDL cholesterol	99 (30)	148 (70)	50 (38-62)	8.7	225	<.001
HDL cholesterol	56 (15)	49 (18)	−7 (−11 to −3)	−4.0	228	<.001
VLDL cholesterol	17 (7)	25 (13)	8 (6-10)	6.7	228	<.001
Non-HDL cholesterol	118 (46)	181 (88)	63 (49-77)	8.9	228	<.001
Triglycerides	96 (110)	154 (179)	58 (9-107)	3.9	232	<.001
ApoB	89 (23)	140 (59)	49 (39-59)	10.1	213	<.001
ApoA-I	149 (29)	152 (31)	4 (−2 to 10)	1.2	214	.23

Abbreviations: ApoA-I, apolipoprotein A-I; ApoB, apolipoprotein B; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

SI conversion factors: To convert HDL, LDL, non-HDL, total, and VLDL cholesterol, multiply by 0.0259; triglycerides, multiply by 0.0113.

*Multivariate repeated measures linear regression model, adjusting for sex, age, weight (age-adjusted percentile), and fat/protein plus carbohydrate ratio of ketogenic diet.

†Statistics are based on the multivariate regression model and test whether the mean difference is different from zero.

Table 2. Mean Plasma Levels of Lipids, Lipoproteins, and Apolipoproteins at Baseline and 6 Months in Patients Receiving the Ketogenic Diet (5). Reproduced with permission from the Journal of the American Medical Association.

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