Journal of Child Neurology

http://jcn.sagepub.com/

Prospective Study of the Modified Atkins Diet in Combination With a Ketogenic Liquid Supplement During the Initial Month

Eric H. Kossoff, Jennifer L. Dorward, Zahava Turner and Paula L. Pyzik

J Child Neurol published online 10 September 2010
DOI: 10.1177/0883073810375718

The online version of this article can be found at:
http://jcn.sagepub.com/content/early/2010/09/07/0883073810375718

Published by:

http://www.sagepublications.com

Additional services and information for *Journal of Child Neurology* can be found at:

Email Alerts: http://jcn.sagepub.com/cgi/alerts

Subscriptions: http://jcn.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

Downloaded from jcn.sagepub.com at WELCH MEDICAL LIBRARY on September 14, 2010

Journal of Child Neurology
000(00) 1-5
© The Author(s) 2010
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/0883073810375718
http://jcn.sagepub.com
SAGE

Prospective Study of the Modified Atkins Diet in Combination With a Ketogenic Liquid Supplement During the Initial Month

Eric H. Kossoff, MD[1], Jennifer L. Dorward, RD[1], Zahava Turner, RD[1], and Paula L. Pyzik, BA[1]

Abstract

The modified Atkins diet is a high-fat, low-carbohydrate treatment for intractable childhood epilepsy. As data suggest that a stricter diet onset can be more effective, we added a ketogenic supplement to the modified Atkins diet during its initial month. Thirty children with intractable epilepsy were prospectively started on the modified Atkins diet in combination with a daily 400-calorie KetoCal® shake. At 1 month, 24 (80%) children had >50% seizure reduction, of which 11 (37%) had >90% seizure reduction. There was no significant loss of efficacy during the second month after KetoCal® was discontinued. The use of this ketogenic supplement increased daily fat intake and thus the ketogenic ratio (1.8:1 versus 1.0:1 in the modified Atkins diet alone, $P = .0002$), but did not change urinary or serum ketosis. The addition of a ketogenic supplement to the modified Atkins diet during its initial month appears to be beneficial.

Keywords

epilepsy, diet, ketosis, ketogenic, Atkins, KetoCal®

Received April 28, 2010. Received revised May 21, 2010. Accepted for publication May 21, 2010.

The modified Atkins diet was first described in 2003 as a less restrictive, outpatient-initiated dietary treatment for children and adults with intractable epilepsy.[1] Designed to mimic the ketogenic diet, it creates a ketotic state by providing high-fat and low-carbohydrate foods, but unlike the ketogenic diet, it does not restrict protein, calories, or fluid. Since its introduction, it has been studied in a 129 patients with epilepsy from 8 countries in total to date.[1-13]

Although there are advantages compared with the ketogenic diet, the percentage of children with >50% seizure reduction after 6 months in combined prospective trials of the modified Atkins diet is slightly less, 46% versus 56%.[2-4,11,13,14] One possible explanation for the lower efficacy could be a less strict initiation period in comparison to the ketogenic diet. Although evidence suggests that initial fasting is not necessary for long-term seizure control, research does demonstrate that higher ketogenic ratios of fat:carbohydrate plus protein (4:1 versus 3:1) are more effective when starting the ketogenic diet and lower carbohydrate limits are more effective (10 versus 20 grams per day) when starting the modified Atkins diet.[4,15] After 3 months of dietary treatment, neither a 4:1 ratio nor a 10 gram per day carbohydrate limit needed to be maintained for long-term seizure control in these studies.[4,15]

KetoCal® (Nutricia in North America, and SHS in Europe), is a milk protein–based, powdered formula with a mild vanilla flavor to which water is added, available in either a 3:1 or 4:1 ratio. It is most often used as an infant or gastrostomy tube formula for children on the ketogenic diet, but can be ingested orally. The powder can also be used as a flour substitute in recipes. Two studies suggest that formula-only ketogenic diets could have improved efficacy over a solid-food ketogenic diet.[16,17]

We hypothesized that supplementing the modified Atkins diet with a daily ketogenic formula (KetoCal®) would lead to improved seizure control and tolerability, possibly due to increased ketosis. Our secondary hypothesis was that achieved seizure reduction would be maintained during the second month, even after KetoCal® was discontinued, thus confirming that early restrictiveness is only necessary temporarily.

[1] The John M. Freeman Pediatric Epilepsy Center, Departments of Neurology and Pediatrics, Johns Hopkins Medical Institutions, Baltimore, MD

Corresponding Author:
Eric H. Kossoff, MD, Suite 2158, 200 North Wolfe Street, David M. Rubenstein Child Health Building, The John M. Freeman Pediatric Epilepsy Center, The Johns Hopkins Hospital, Baltimore, MD 21287
Email: ekossoff@jhmi.edu

Downloaded from jcn.sagepub.com at WELCH MEDICAL LIBRARY on September 14, 2010

Methods

An open-label, nonblinded, prospective study design was used. The basic modified Atkins diet protocol was designed to be identical to previously published information,[2] with the exception of the supplemental KetoCal®. Thirty children with epilepsy were evaluated in the Johns Hopkins Hospital outpatient pediatric epilepsy clinic by the primary investigator (E.K.) and dietitian (J.D.) at all study visits.

Inclusion criteria included age 3–18 years, prior use of at least 2 anticonvulsants, and at least daily, countable seizures. No child with prior use of the modified Atkins diet for more than 2 days or any use of KetoCal® was enrolled, nor were patients with known hypercholesterolemia, kidney dysfunction, or heart disease. Children significantly underweight (body mass index <3% for age) or with significant aversion to milkshakes were also not included. No child who was currently on the traditional ketogenic diet was enrolled; however, use of the ketogenic diet >1 year before enrollment was allowed. Children were evaluated at baseline, and 1 and 2 months in clinic, with intermittent contact by means of phone and email in between. After the study concluded, families were allowed to continue contact and the modified Atkins diet if desired, with follow-up arranged.

After the initial visit, a prescription was given to families to obtain a fasting complete blood count, lipid profile, and comprehensive metabolic profile (liver and kidney functions) at their local laboratory. Parents were asked to fill out a 3-day food record of typical prediet meals. Diet composition was analyzed using Food Processor for Windows® (EHSA Research, Salem, Oregon) and averaged over a 3-day period. Copies of *The CalorieKing Calorie, Fat and Carbohydrate Counter* and a box of home urine ketosis strips were given to all families free of charge.[18] Carbohydrates were limited to 10 grams per day and high-fat foods described and encouraged. All families were told to start a carbohydrate-free multivitamin and calcium supplement if not currently receiving them. A monthly calendar was provided, with instructions to document seizures daily, morning urine ketosis semiweekly, and weight weekly. Anticonvulsant medications were not changed throughout the 2-month study period.

Families were provided with a single case containing 6 identical cans of KetoCal® 4:1, each of which contained 300 grams of powder. Instructions were given to mix 8 ounces (240 mL) of warm water with two-thirds of a cup (60 grams) of KetoCal® powder to create a 10-ounce (300 mL), approximately 400-calorie, "milkshake." The milkshake could be additionally flavored with carbohydrate-free syrups or gelatin if desired and also refrigerated. If the child refused to drink the milkshake, the powder could be mixed into foods or baked with using recipes available on the Internet. Families had to ensure that the 60-gram KetoCal® powder allotment was ingested fully over a single day, but its timing was flexible. Although we recommended substituting the milkshake for a meal (eg, lunch) to divide carbohydrates over breakfast and dinner, families could alternatively give it as an extra snack or divide the shake throughout the day.

At the 1-month clinic visit, daily KetoCal® was discontinued and families told to discard any remaining powder. Families were asked to rate the ease of the modified Atkins diet using a 10-point scale (with 10 being the easiest) as well as the taste of KetoCal® (with 10 being the most enjoyed). All laboratory test results were repeated with an inclusion of serum beta-hydroxybutyrate.

At the 2-month clinic visit, the study ended and families were given the choice to continue or stop the modified Atkins diet. Laboratory studies and ratings of the modified Atkins diet were repeated. At this time, anticonvulsants could be adjusted, the daily carbohydrate limit increased to 15 grams per day, or KetoCal® restarted by prescription per family request.

Categorical data were analyzed using the Fisher exact test, and medians were compared using Wilcoxon 2-sample test. Means were compared using a 2-sample 2-tailed t test and correlation between variables using a Pearson rho test. The study was approved by the Johns Hopkins institutional review board and listed at www.clinicaltrials.gov (NCT00681239). Informed consent was obtained from all parents and additional assent from any adolescents. The significance level for all tests was $P = .05$.

Results

Subject Demographics

Thirty children, 19 (63%) female, were treated from June 2008 to September 2009, and all successfully completed all 3 study visits. The median age at study onset was 7 years (range: 3–16 years) with seizures starting at 3 years (range: 0.2–12 years). The median number of current anticonvulsants was 2 (range: 0–4), with 5 (range: 2–13) attempted before enrollment. Two children had tried the ketogenic diet years prior; 5 had active vagus nerve stimulation. The median number of seizures per week was 70 (range: 7–700 per week), and seizure types included myoclonic (n = 11), complex partial (n = 7), absence (n = 6), atonic (n = 5), and myoclonic-absence (n = 1). Etiologies when known included absence epilepsy (n = 6), myoclonic-astatic epilepsy (Doose syndrome) (n = 5), Lennox-Gastaut syndrome (n = 2), Dravet syndrome (n = 1), stroke (n = 1), Gastaut occipital epilepsy (n = 1), Jeavon syndrome (n = 1), juvenile myoclonic epilepsy (n = 1), left temporal lobe epilepsy (n = 1), and Angelman syndrome (n = 1).

Seizure Reduction

At the 1-month visit, 24 subjects (80%) had >50% seizure improvement, of which 11 (37%) were >90% improved including 4 (13%) seizure-free. After 2 months, 21 (70%) were >50% improved, of which 13 (43%) were >90% improved including 3 (10%) were seizure-free. Six (20%) parents perceived there was an increase in seizures immediately after KetoCal® was discontinued. At the end of the study, 23 (77%) decided to remain on the modified Atkins diet. Three families chose to discontinue the modified Atkins diet and pursue other options. Four families decided to switch to the ketogenic diet, of which 2 had a reported 25% additional reduction in seizures, 1 became seizure-free, and 1 had no additional improvement.

Similar to previous pediatric studies of the modified Atkins diet, there was no correlation between age at diet onset or seizure onset, number of anticonvulsants attempted or at diet onset, seizure type, seizure frequency, or weight loss with likelihood of a >90% seizure reduction at 1 month. There was no correlation between large urinary ketosis and >90% seizure reduction, with 7 of 12 (58%) of those with >90% seizure reduction having large urinary ketosis and 9 of 18 (50%) of those with <90% reduction also having large ketosis ($P = .47$). Male gender was slightly more likely to have a >90%

Downloaded from jcn.sagepub.com at WELCH MEDICAL LIBRARY on September 14, 2010

Table 1. Mean Daily Dietary Intake in Study Subjects at Baseline, After 1 Month in Study Patients, and in Comparison to Previous Food Analysis of the Modified Atkins Diet Using 10 Grams of Carbohydrate per Day Limit[a]

Diet Composition	Baseline	Modified Atkins Diet Plus KetoCal®	Modified Atkins Diet Alone[4]	*P* Value[a]
Ketogenic ratio	0.3:1	1.8:1	1.0:1	.0002
Fat (grams)	80	195	114	.0001
Carbohydrates (grams)	240	15	10	.001
Protein (grams)	74	101	107	.61
Calories	1,937	2,290	1,572	.0008

[a] *P* value compares the modified Atkins diet plus KetoCal® to the modified Atkins diet alone.

seizure reduction (7 of 12 (58%) versus 4 of 18 (22%), $P = .05$). The 2 children with previous ketogenic diet exposure (2–3 years prior using a 4:1 ratio) both had a 50%–90% reduction in seizures, similar to their prior results with the ketogenic diet.

Ketosis

Urinary ketosis was achieved in all patients within several days of starting the diet. After 1 month, large urinary ketosis was reported in 16 (53%), moderate in 8 (27%), and small in 6 (20%). This was not different than previous reports of the modified Atkins diet alone after 1 month, in which approximately 75% of treated children had moderate to large ketosis.[2-4,13] The median fasting serum beta-hydroxybutyrate was 2.4 mmol/L (range: 0.7–38.5 mmol/L).

At the 2-month visit, after KetoCal® had been discontinued for 1 month, there was no decrease in the number of subjects with large urinary ketosis (14 of 30, 47%; $P = .40$) or serum beta-hydroxybutyrate (median 3.0 mmol, range: 0.1–48.1; $P = .90$). Seven children had a reported increase in reported urinary ketosis between study visits. There was no correlation between urinary or serum ketosis and either >50% or >90% seizure reduction at either time point.

Modified Atkins Diet and KetoCal® Tolerability

Parents were asked to rate the ease of use of the modified Atkins diet at each study visit. The mean score did not significantly change over time, 7.2 versus 7.1, $P = .95$. Ten families increased their rating score between visits, 10 decreased, and 10 remained unchanged.

Overall, KetoCal® was well-tolerated and all children reportedly ingested the allotted daily amounts for the initial month. Twenty-six (87%) drank the supplement as milkshakes, of which 3 (12%) reported having to flavor the milkshake to improve taste. Only 4 children refused the milkshakes completely, and these parents then mixed the powder into foods or made "muffins"; these children did equally well with similar ketosis as those drinking a milkshake. The mean KetoCal® rating was 5.3 of 10 (standard error of the mean = 0.5). There was no clear correlation between KetoCal® rating and modified Atkins diet ratings ($r = 0.08$), the age of the child ($r = -0.12$), or gender ($P = .47$). Parental rating of KetoCal® taste and 1-month diet tolerability also did not correlate with seizure reduction. Fourteen (47%) chose to restart KetoCal® at study conclusion; 6 due to perceived seizure worsening as described previously and 8 due to improved convenience and taste.

Diet Analysis

Similar to previous data, the baseline ketogenic ratio before starting the diet was 0.3:1.[4] Calories increased overall from baseline during the first month by a mean of 353 kilocalories (1937 to 2290 kilocalories, $P = .06$), nearly the amount of the daily KetoCal® milkshake. At 1 month, independent of supplemental KetoCal®, the mean daily intake of children was 154 grams of fat, 15 grams of carbohydrate per day, with a 1.5:1 ketogenic ratio. There was no significant change in the second month dietary composition, including an identical 1.5:1 ketogenic ratio ($P = .87$).

Compared with the previous information reported using a 10 gram of carbohydrate per day modified Atkins diet alone, there were significant differences for our subjects (Table 1).[4] The ketogenic ratio nearly doubled, from a mean of 1.0:1 to 1.8:1 ($P = .0002$), which is closer to the 3:1 or 4:1 traditional ketogenic diet ratio. Of interest, carbohydrate intake also increased from 10 to 15 grams/day, despite our recommendations to limit to 10 grams per day. As protein remained constant, the ratio increase was solely due to a mean 74% increase (81 grams) in daily fat intake ($P = .0001$). This cannot be fully explained by the supplemental milkshake, which contains 40 grams of fat. Even excluding the KetoCal® milkshake from the 1-month diet analysis, there was a significant increase in both mean ketogenic ratio (1.5:1; $P = .007$) and fat intake (155 grams/day; $P = .04$).

Adverse Effects

Over the 2-month study period, the average change in weight was -0.9 kg, with a range of -9.0 to 2.2 kg. The mean starting weight was 34.1 kg and decreased to 33.2, $P = .84$. Eleven children gained weight during the study period. Specific adverse events reported included constipation (n = 2), initial fatigue (n = 2), hair thinning (n = 1), and bruising (n = 1). No child had increased seizures compared with baseline during the study period. Baseline and 2-month serum laboratory values were compared (Table 2). There was a significant increase in total

Downloaded from jcn.sagepub.com at WELCH MEDICAL LIBRARY on September 14, 2010

Table 2. Mean Baseline and 2-Month Serum Laboratory Values

Laboratory Value	Baseline	2-Month	*P* Value
Alanine aminotransferase (IU/L)	17.8	19.8	.23
Aspartate aminotransferase (IU/L)	27.1	26.1	.73
Blood urea nitrogen (mg/dL)	14.0	15.7	.19
Creatinine (mg/dL)	0.5	0.5	.31
Total cholesterol (mg/dL)	172.7	217.4	.002
High-density lipoprotein cholesterol (mg/dL)	57.5	57.7	.97
Low-density lipoprotein cholesterol (mg/dL)	100.1	142.2	.002
Triglycerides (mg/dL)	76.2	90.5	.14

and low-density lipoprotein cholesterol, and a trend toward an increase in blood urea nitrogen and triglycerides.

Discussion

Our results support previous findings that a strict initiation period to the modified Atkins diet is advantageous for seizure control.[4] A potential method to increase strictness by using a daily ketogenic supplement appeared to be effective, as hypothesized. Although not a true control group, when compared with results from published studies of the modified Atkins diet alone, of which 4 studies included 1-month outcomes, the likelihood of a >50% response was higher (37 of 64, 58%, $P = .03$) as well as trend seen toward more children with >90% response (12 of 64, 19%, $P = .05$).[2-4,11] In addition, we found that the supplement need not be continued beyond the first month.

Why did the ketogenic supplement help? Although we predicted KetoCal® would improve ketosis, it did not clearly do so. Our results suggest that a high daily fat intake could be critical to the mechanism of action of dietary therapies. Increasing the ketogenic ratio has been shown to be important for the ketogenic diet and some have also theorized that extra fat could be the mechanism by which dietary treatments are effective in both humans and animals.[15,19] Contrarily, caloric restriction, theorized by some as a mechanism of action for dietary treatments, did not appear to be important.

There are several limitations to this study. There was no control group of either the modified Atkins diet alone (without supplementation) or continued anticonvulsant management without dietary intervention. Second, it is possible other available ketogenic diet supplements such as medium-chain triglyceride oil or KetoVolve® (Solace Nutrition, Rockville, MD) could have similar benefits. Providing additional nutritional guidance to ensure a high fat intake while on the modified Atkins diet might be helpful without the need for a supplement. This can be important for some families as the approximate cost of the KetoCal® for 1 month is $150, which is typically not reimbursed by insurance companies in the United States for orally feeding children.

Future directions include determining if additional methods to make the modified Atkins diet stricter with even higher fat content during the initial month would be even more beneficial for seizure control. Theoretical options include a brief initial fasting period, larger daily quantities of KetoCal®, or dividing the KetoCal® throughout the day to stabilize ketosis as has been suggested.[3] Additional methods to possibly clarify if higher ketogenic ratios are responsible for the improved efficacy could include different KetoCal® formulations using different ketogenic ratios (eg, 2:1 or 3:1).

In summary, the addition of daily ketogenic formula supplementation (KetoCal®) to the modified Atkins diet during its initial month of use appears to improve its efficacy for the treatment of intractable childhood epilepsy. Our results suggest that the high fat content of dietary treatments could be of primary clinical importance. This study also provides further evidence that a strict, high-fat starting period is only necessary for the initial month.

Author Contributions

EHK was the primary investigator, neurologist, and designer of the study protocol. EHK wrote the manuscript. JLD was the primary dietitian for patient care and a coinvestigator. ZT was a secondary dietitian for the study and coinvestigator. PLP was the research coordinator for this study. All authors reviewed and commented upon the manuscript.

Declaration of Conflicting Interests

The authors declared a potential conflict of interest (e.g. a financial relationship with the commercial organizations or products discussed in this article) as follows: Dr. Kossoff has received consultant fees from Nutricia, Inc., and Atkins Nutritionals, Inc., unrelated to this research.

Financial Disclosure/Funding

The authors disclosed receipt of the following financial support for the research and/or authorship of this article: this study was supported by an investigator-initiated grant from Nutricia, Inc., who had no influence over data collection, analysis, or the writing of the manuscript.

References

1. Kossoff EH, Krauss GL, McGrogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy. *Neurology*. 2003;61:1789-1791.
2. Kossoff EH, McGrogan JR, Bluml RM, Pillas DJ, Rubenstein JE, Vining EP. A modified Atkins diet is effective for the treatment of intractable pediatric epilepsy. *Epilepsia*. 2006;47:421-424.
3. Kang HC, Lee HS, You SJ, Kang DC, Ko TS, Kim HD. Use of a modified Atkins diet in intractable childhood epilepsy. *Epilepsia*. 2007;48:182-186.
4. Kossoff EH, Turner Z, Bluml RM, Pyzik PL, Vining EP. A randomized, crossover comparison of daily carbohydrate limits using the modified Atkins diet. *Epilepsy Behav*. 2007;10:432-436.
5. Carrette E, Vonck K, de Herdt V, et al. A pilot trial with modified Atkins' diet in adult patients with refractory epilepsy. *Clin Neurol Neurosurg*. 2008;110:797-803.
6. Chapman K, Cardenas JF. Hemimegalencephaly in a patient with a neurocutaneous syndrome. *Semin Pediatr Neurol*. 2008;15:190-193.

Downloaded from jcn.sagepub.com at WELCH MEDICAL LIBRARY on September 14, 2010

7. Ito S, Oguni H, Ito Y, Ishigaki K, Ohinata J, Osawa M. Modified Atkins diet therapy for a case with glucose transporter type 1 deficiency syndrome. *Brain Dev*. 2008;30:226-228.
8. Kossoff EH, Dorward JL, Molinero MR, Holden KR. The modified Atkins diet: a potential treatment for developing countries. *Epilepsia*. 2008;49:1646-1647.
9. Kossoff EH, Rowley H, Sinha SR, Vining EP. A prospective study of the modified Atkins diet for intractable epilepsy in adults. *Epilepsia*. 2008;49:316-319.
10. Kumada T, Miyajima T, Kimura N, et al. Modified Atkins diet for the treatment of nonconvulsive status epilepticus in children. *J Child Neurol*. 2010;25:485-489.
11. Porta N, Vallée L, Boutry E, et al. Comparison of seizure reduction and serum fatty acid levels after receiving the ketogenic and modified Atkins diet. *Seizure*. 2009;18:359-364.
12. Slaughter L, Vartzelis G, Arthur T. New GLUT-1 mutation in a child with treatment resistant epilepsy. *Epilepsy Res*. 2009;84: 254-256.
13. Weber S, Mølgaard C, Karentaudorf, Uldall P. Modified Atkins diet to children and adolescents with medical intractable epilepsy. *Seizure*. 2009;18:237-240.
14. Kossoff EH, Zupec-Kania BA, Rho JM. Ketogenic diets: an update for child neurologists. *J Child Neurol*. 2009;24:979-988.
15. Seo JH, Lee YM, Lee JS, Kang HC, Kim HD. Efficacy and tolerability of the ketogenic diet according to lipid:nonlipid ratios—comparison of 3:1 with 4:1 diet. *Epilepsia*. 2007;48:801-805.
16. Kossoff EH, McGrogan JR, Freeman JM. Benefits of an all-liquid ketogenic diet. *Epilepsia*. 2004;45:1163.
17. Hosain SA, La Vega-Talbott M, Solomon GE. Ketogenic diet in pediatric epilepsy patients with gastrostomy feeding. *Pediatr Neurol*. 2005;32:81-83.
18. Borushek A. *The CalorieKing Calorie, Fat and Carbohydrate Counter*. Hudsonville, MI: Family Health Publications; 2008.
19. Bough KJ, Chen RS, Eagles DA. Path analysis shows that increasing ketogenic ratio, but not beta-hydroxybutyrate, elevates seizure threshold in the rat. *Dev Neurosci*. 1999;21:400-406.

Downloaded from jcn.sagepub.com at WELCH MEDICAL LIBRARY on September 14, 2010