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FULL-LENGTH ORIGINAL RESEARCH

A prospective study of the modified Atkins diet for intractable epilepsy in adults

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SUMMARY

Purpose: **The ketogenic diet is not typically offered to adults with epilepsy due to the significant lifestyle alterations needed for its use. The modified Atkins diet has been recently demonstrated to be therapeutic for children without the need for an admission, fasting period, weighing of foods, or fluid, calorie, and protein restriction.**

Methods: **A prospective, open-label study was performed of adults over 18 years of age, having at least weekly seizures and prior use of at least two anticonvulsants. Carbohydrates were initially restricted to 15 g/day, fats were encouraged, and fluids, protein, and calories were allowed ad lib.**

Results: **Thirty patients, with age ranging from 18 to 53 years, were enrolled. Using an intent-to-treat analysis, 47% had a >50% seizure reduction after 1 and 3 months on the diet; 33% after 6 months. In those with seizure reduction, the median time to improvement was 2 weeks (range: 1–8 weeks). The mean weight loss was 6.8 kg, $p < 0.001$. Body-mass index (BMI) decrease correlated with efficacy at 3 months, $p = 0.03$. Ten subjects (30%) discontinued the diet prior to 3 months. Side effects included increased cholesterol (mean 187 to 201 mg/dL), blood urea nitrogen (BUN; 13 to 16 mg/dL), and urine calcium to creatinine ratio (0.14 to 0.19).**

Conclusions: **A modified Atkins diet appears to demonstrate preliminary efficacy for adults with intractable epilepsy, especially in those who lost weight. Considering the rapid response in those who improved, but somewhat high discontinuation rate, a 2-month trial period may be adequate to assess for efficacy.**

KEY WORDS: **Ketogenic, Atkins, Adults, Epilepsy, Ketosis, Diet.**

The ketogenic diet is an established nonpharmacologic therapy for children with intractable epilepsy (Kossoff, 2004). It can be restrictive and time-intensive, with foods prescribed by a trained dietitian and weighed and measured carefully by the family in order to induce a ketotic state. Although its successful use in 100 adults was reported (Barborka, 1930), only one other series of 11 adults has been reported since (Sirven et al., 1999). Both studies described nearly identical responder rates of 56% and 54%, respectively (Barborka, 1930; Sirven et al., 1999), which is also remarkably similar to most studies of children (Henderson et al., 2006). However, the ketogenic diet is rarely offered to adults due to perceived inefficacy and restrictiveness.

The modified Atkins diet induces ketosis, but without fluid, calorie, or protein restriction, nor the requirement for fasting, food weighing, or hospitalization (Kossoff et al., 2003, 2006, 2007a; Kang et al., 2007). Now in 68 children to date, efficacy has been similar to the ketogenic diet (Kossoff et al., 2003, 2006, 2007a; Kang et al., 2007). We hypothesized that the modified Atkins diet would be also an effective therapy for adults with intractable epilepsy, as defined as a failure to respond to at least two anticonvulsant medications. In addition, the potential for weight loss may provide added incentive for patients with epilepsy and comorbid obesity (Foster et al., 2003).

METHODS

A prospective, open-label study design was employed. Subjects were 18 years of age or older, had tried at least two anticonvulsants, with at least weekly seizures. Patients

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with prior use of the Atkins diet for more than 7 days or the ketogenic diet within the past year were not included. Adults with hypercholesterolemia, cardiovascular, or renal disease were excluded. Patients significantly underweight (body mass index < 18.5), with status epilepticus within the past 6 months, antiepileptic therapy changes (medication, vagus nerve stimulation, or surgery) within the past 6 months, a 2-week period of seizure freedom within the past 2 months, or nonepileptic seizures were also excluded from participation. The study was approved by the Johns Hopkins institutional review board and General Clinical Research Center.

Patients were evaluated at baseline, 1, 3, and 6 months on the diet. A baseline fasting complete blood count, lipid profile, electrolytes and liver functions, urine calcium and creatinine, and urine hcG (for women) were obtained at each visit. Patients provided a 3-day food record at each visit. *Dr. Atkins New Diet Revolution* and *The CalorieKing Calorie, Fat and Carbohydrate Counter* were given to all subjects (Atkins, 2002; Borushek, 2006).

All patients were instructed to limit carbohydrates to 15 g/day, fluids and calories were ad lib, and high fat foods were encouraged. Patients were told to take a daily multivitamin and calcium supplement. Subjects were instructed to document seizures daily, urine ketones semiweekly, and weight weekly. Many patients requested to lose weight, which was encouraged for those who were clinically obese at a rate no higher than 1 kg/week approximately. Medication and carbohydrate limit changes were made only after the first month.

Categorical data were analyzed using Fisher's exact test and medians were compared using a Wilcoxon two-sample test. Means were compared using a paired two-sample *t*-test. The significance level for all tests was $p = 0.05$.

Results

Demographics

Thirty patients were enrolled and treated from November 2004 to November 2006; one patient consented but did not start the diet. Nineteen patients (63%) were female; the median age was 31 years (range: 18–53 years). The median seizure frequency was 10 per week (range: 1–140 seizures per week). The median number of anticonvulsants attempted was 8 (range: 2–14), 12 (40%) had vagus nerve stimulators implanted, and 8 (27%) had prior epilepsy surgery. Twenty-three (77%) had complex partial seizures, five had multiple seizure types, and two had absence seizures. Subjects had localization to the temporal lobe (8), frontal lobe (7), tuberous sclerosis complex (multifocal) (2), and occipital lobe (1) when a focus was identified.

Efficacy

Outcomes are described using intent-to-treat analysis (Table 1). In the 18 patients in whom any improvement occurred, the median time until seizure reduction was 2 weeks (range: 1–8 weeks). Eight patients reduced medications; five successfully. Twenty-six (87%) subjects remained on the diet after 1 month, 20 (67%) after 3 months, and 14 (47%) completed the 6-month study. All 14 subjects who finished the 6-month study chose to continue the diet afterwards. Of the 16 who discontinued prior to study completion, nine (56%) did so due to inefficacy, six (38%) due to restrictiveness, and one subject did not start after initially consenting.

Table 1. Seizure reduction as assessed at clinic visits using an intent-to-treat analysis

Clinic visit	No improvement	1–50%	51–75%	76–99%	Seizure-free
1 month	15 (50%)	1 (3%)	10 (33%)	4 (14%)	0 (0%)
3 months	14 (47%)	2 (6%)	7 (24%)	6 (20%)	1 (3%)
6 months	15 (50%)	5 (17%)	6 (20%)	3 (10%)	1 (3%)

The influence of patient demographics on 3-month outcomes is listed in Table 2. A trend was noted for higher initial seizure frequency with an improved likelihood of a >50% seizure reduction at 3 months ($p = 0.06$). The four subjects with the highest initial seizure frequency (range: 30–140 seizures per week) were the best responders at 1 month, with all having at least a 76% seizure reduction. Over the subsequent 5 months, however, this difference became less pronounced as several other subjects with less initial seizure frequencies demonstrated equivalent outcomes. At 3 months, 10 of 23 (43%) patients with less than an initial median seizure frequency of 20 seizures per week were >50% improved.

Table 2. Prediet demographics and their influence on diet efficacy at 3 months. Values are expressed as median (range) or number (percentage)

Patient demographic	>50% seizure reduction (n = 14)	<50% seizure reduction (n = 16)	p value
Age of first seizure (years)	12.5 (0–34)	8.0 (0.5–44)	0.27
Age of starting the diet (years)	28.5 (18–39)	36.5 (19–53)	0.10
Anticonvulsants tried	9 (4–14)	7 (2–14)	0.76
Anticonvulsants at diet onset	2 (1–4)	2 (1–4)	0.91
Seizure frequency (per week)	13 (3–140)	3 (1–21)	0.06
Baseline weight (kg)	72 (51–107)	79 (53–124)	0.63
Female gender	8 (57%)	11 (69%)	0.24
Generalized or multifocal epilepsy	3 (21%)	4 (25%)	0.33
Prior resective epilepsy surgery	4 (29%)	4 (25%)	0.31
Concurrent vagus nerve stimulation	7 (50%)	5 (31%)	0.25

Table 3. Diet compositions per day, based on all available food records collected at clinic visits. Values are expressed as medians (range)

Diet attribute	Baseline (n = 18)	1 month on diet (n = 19)
Calories	1866 (580–4890)	1354 (671–2660)
Ratio (fat:protein and carbohydrate grams, *n*:1)	0.2 (0.1–0.6)	0.9 (0.3–2.0)
Carbohydrates (g)	234 (55–526)	20 (3–60)
Protein (g)	66 (26–166)	102 (49–154)
Fat (g)	68 (23–250)	98 (37–218)

Table 4. Changes in mean (standard deviation) laboratory values (mg/dL) over time in patients with follow-up laboratory results (n = 26)

Laboratory value	Baseline	Most recent result	p value
Glucose	84 (8)	83 (11)	0.54
Urine calcium to creatinine ratio	0.14 (0.09)	0.19 (0.14)	0.03
Blood urea nitrogen (BUN)	13 (3)	16 (3)	0.0001
Creatinine	0.8 (0.1)	0.8 (0.2)	0.35
Total protein	7.4 (0.4)	7.4 (0.4)	0.75
Aspartate aminotransferase (AST)	21 (5)	21 (7)	0.88
Total cholesterol	187 (39)	201 (44)	0.05
HDL cholesterol	63 (16)	66 (17)	0.59
LDL cholesterol	102 (37)	120 (44)	0.14
Triglycerides	94 (48)	80 (40)	0.13

Ketosis

All 28 patients on the diet for at least one week became ketotic; 21 (75%) reported large (80–160 mg/dL) urinary ketosis. Sixty-one percent (16 of 26) had moderate-to-large ketosis at 1 month, but only 13% (2 of 15) did at 6 months. At 1 month, 10 of 16 (63%) with moderate-to-large ketosis had >50% seizure reduction, compared to three of 10 (30%) with small or less ketosis, p = 0.11. At 3 and 6 months, there was no trend toward correlation.

Diet composition

Baseline and follow-up diet compositions based on 3-day food records when provided are listed in Table 3. The majority of calories (64%) eaten were from fat. The mean carbohydrate amount per day was 20.0 g at 1 month, with a standard deviation of 10.1 g/day. During the study period, 12 patients in whom the diet was helpful but perceived as restrictive chose to increase carbohydrates from 15 to 20 g/day after either one (3 subjects) or 3 months (9) when given the option by our dietitian (HR). This 5-g increase was confirmed in their subsequent food records provided. None of these 12 patients reported a resultant worsening of seizures or ketosis and they remained on approximately 20 g of carbohydrates per day for the remainder of their study participation.

Of the 18 patients who provided both a baseline and follow-up food record, 12 (67%) reduced caloric intake. The median reduction in calories for those with >50% seizure reduction was 446 calories per day compared to 352 calories per day for those with <50% reduction, p = 0.67. There was also no correlation between the actual mean daily carbohydrates at 1 month and efficacy, with six of nine (67%) eating more than 20 g/day having >50% seizure reduction compared to five of 10 (50%) with fewer than 20 g/day, p = 0.40.

Effect on weight

Patients lost weight from a baseline mean (standard deviation) of 80.2 kg (20.7 kg) to 73.4 kg (15.5 kg) at their final clinic visit, p < 0.001. Body-mass index (BMI) was similarly reduced from a mean (standard deviation) of 28.3 (7.2) to 26.4 (5.5), p < 0.001. The median BMI change was −0.9 (range: 0.6–9.5). At study onset, 11 (37%) were clinically obese (BMI >30) versus seven (23%) at their final clinic visit, p = 0.20. Of the 26 patients with at least one follow-up clinic visit, 22 (85%) lost weight.

There was a correlation between BMI decrease and efficacy. A higher likelihood of >50% response at 3 months was noted in those with greater than the median BMI decrease of −0.9 (10 of 15, 67%) compared to subjects with less BMI decrease (4 of 15, 27%), p = 0.03. However, two of the three subjects who had a BMI increase over the course of the study had >50% seizure reduction at 3 months.

Side effects

Laboratory results are listed in Table 4. No patient discontinued the diet due to abnormal laboratory results or increased seizure frequency. Constipation, kidney stones, and irregular menses were not reported. Total cholesterol increased from 187 to 201 mg/dL (p = 0.05). The follow-up mean LDL cholesterol results (120 mg/dL, normal <130 mg/dL), HDL cholesterol (66 mg/dL, normal >60 mg/dL), and triglycerides (80 mg/dL, normal <150 mg/dL) were all in the average risk ranges (Gluckman et al., 2004). One patient reported leg swelling after 3 months that resolved spontaneously within 1 month without any dietary or medication changes; another subject felt lethargic and discontinued the diet after 2 weeks.

Discussion

The results of this small, prospective study provide preliminary evidence for some benefit of the modified Atkins diet for adults with intractable epilepsy. To the authors' knowledge, this represents the largest evaluation of any dietary therapy for epilepsy in adults in 77 years (Barborka, 1930). Considering that approximately 30–40% of patients with epilepsy are refractory to anticonvulsants, many of

whom are not surgical candidates due to generalized or multifocal epilepsy or possible functional risk, there is a need for further therapies (Kwan and Brodie, 2000).

Although the results were modest, the seizure reduction from the diet was similar to most trials of adjunctive anticonvulsants for adults with intractable epilepsy, with 33–47% of patients having >50% seizure reduction over the study period (Marson et al., 1997; Cramer et al., 1999). The modified Atkins diet, however, offers several advantages over anticonvulsants due to its lack of drug interactions, rapid initiation, and relative absence of both personal and insurance-related financial barriers to its use (Kossoff, 2004). No subject characteristics predicted diet response, including the previously reported concurrent vagus nerve stimulation, although those with higher initial seizure frequency had slightly better outcomes (Kossoff et al., 2007b). Similar to studies of children (Kossoff et al., 2006, 2007a; Kang et al., 2007), there was only a slight, early correlation between level of ketosis and efficacy, which is worthy of future study with the traditional ketogenic diet as well.

The modified Atkins diet was well tolerated and most patients were motivated to continue it as long as seizures were reduced. The increase in total cholesterol (Kwiterovich et al., 2003; Kossoff et al., 2007a), blood urea nitrogen (BUN; Kossoff et al., 2006), and urine calcium to creatinine ratio (Furth et al., 2000) have been previously reported and did not lead to diet discontinuation. Cholesterol and triglyceride levels were all generally within the normal range while on the diet (Gluckman et al., 2004). Weight loss was often purposeful and a greater BMI decrease was surprisingly correlated with efficacy at 3 months, unlike previous studies in children (Kossoff et al., 2006, 2007a). Most patients were able to keep carbohydrates within the prescribed amount. The diet was slightly more likely to be helpful in those with higher initial seizure frequencies and younger ages, but not any particular seizure type. The long-term use of the Atkins diet for adults with obesity has been reported as safe, although studies are limited (Bravata et al., 2003).

There are several limitations to this study. It is possible that the results could represent a placebo effect or regression to the mean with this small study population. In addition, although prospective, there was no control group or observer blinding. Subjects may have been more compliant with medications due to the nature of participating in a prospective study. Lastly, it is possible that actual dietary intake was different than recommended, as we had to rely on patient-provided food records rather than direct observation.

In summary, this preliminary study suggests that in a manner similar to children, the modified Atkins diet may be a helpful new treatment option for adults with intractable epilepsy. It may be especially appropriate in situations of comorbid obesity. Further controlled studies are necessary and warranted. Improvement typically occurred rapidly when present; therefore the diet could possibly be discontinued after 2 months if ineffective and perceived by the patient as restrictive.

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