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Ketogenic diet in adolescents and adults with epilepsy

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ABSTRACT

Purpose: The ketogenic diet is an alternative treatment for patients with refractory epilepsy. Most studies to date report dietary response in children. There are limited data evaluating the efficacy of the ketogenic diet in adults. This is a report of the long-term outcome in a largely adult population of patients treated with the ketogenic diet for epilepsy.
Method: Twenty-nine adult and adolescent patients (mean age 32 years, range 11–51) were initiated on the ketogenic diet and followed until diet discontinuation. Clinical response and adverse effects were noted during the duration of the diet.
Results: Fifty-two percent of patients had a significant reduction in seizure frequency on the ketogenic diet, including 45% with ≥50% reduction in seizure frequency. Thirty-one percent had no improvement, seven percent were unable to successfully initiate the diet, and 10% had a >50% increase in seizure frequency. The diet was continued for a mean of 9 months (range 0.13–35 months), with five patients completing ≥23 months. There was a trend toward better response and better tolerability/longer duration in patients with symptomatic generalized epilepsy. The diet was generally well-tolerated, but undesired weight loss and constipation were the most frequent adverse effects.
Conclusion: The ketogenic diet can be used safely in the adult and adolescent population, with a response rate similar to those seen in children. Patient with symptomatic generalized epilepsy may be particularly good candidates for this type of dietary treatment.

1. Introduction

The ketogenic diet is an alternative form of treatment for patients with refractory epilepsy. Approximately 40–67% of pediatric patients may experience a ≥50% seizure frequency reduction, and multiple seizure types may respond.[1–3] Only limited data regarding the utility of the ketogenic diet in adults are available.[4–9] Long-term data regarding the response to the ketogenic data in adults are lacking at this time.

We report the long-term data on a series of twenty-nine patients (ages 11–51 years), who were initiated on the ketogenic diet at the Jefferson Comprehensive Epilepsy Center.

2. Materials and methods

All patients who were initiated on the ketogenic diet for refractory epilepsy and followed until diet discontinuation at the Jefferson Comprehensive Epilepsy Center were included. Patients were placed on the ketogenic diet (ratio of 4 g fat: 1 g combined carbohydrates and protein) utilizing methods described previously.[5] All diets were initiated in the hospital after an initial period of fasting for 24–48 h. On-going dietary consultation was provided through telephone and e-mail. All patients had monitoring of the complete blood count, liver function tests, lipid panel, electrolytes, selenium, carnitine, and EKG testing. The maximum duration of treatment was recommended to be 24 months, due to a concern for potential complications of a long-term high-fat diet. Antiepileptic medications were not changed during a minimum of 3 months after diet initiation. Afterwards, medications changes were made at the discretion of the patient's physician.

Seizure type and frequency at baseline was the mean seizure frequency for each seizure type during the 3 months prior to diet

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initiation. Seizure type and frequency per month was then recorded at each follow-up evaluation. Dietary compliance was evaluated through patient and caretaker history and evaluation of urinary ketones, which were logged daily.

3. Results

3.1. Patients

Twenty-nine patients (16 women, 13 men) with refractory epilepsy (14 symptomatic generalized, 11 focal, 4 idiopathic generalized) were initiated on the ketogenic diet. Patients classified as having symptomatic generalized epilepsy had cognitive impairment, generalized tonic–clonic seizures, and a varied combination of other types of seizures (which included atypical absence, tonic, atonic, myoclonic, and complex partial) and generalized epileptiform abnormalities on EEG. All patients were ≥17 years at the time of diet initiation, except one (11 years). The mean age of the patients was 32 years at diet initiation. Each patient had tried a mean of 6.4 (range 3–16) AEDs and five had prior epilepsy surgery. Mean baseline seizure (all types) frequency was 104 seizures per month (range 0.33–600, SD 167; median 27).

All patients transitioned to the ketogenic diet within two to five days (mean 2.4 days to first positive urinary ketones, SD 2.3) except for two patients, who were unable to continue the diet due to a metabolic acidosis in one and abdominal pain in another. Patients continued the diet for a mean of 9 months (range 0.13–35 months). Five patients completed ≥23 months of the diet. Three patients elected to remain on a high fat diet after ketogenic diet completion, which included a significant but non-uniform increase in dietary protein and carbohydrate.

3.2. Response to diet

Fifteen (52%) of patients had a reduction in their seizure frequency. Thirteen patients (45%) had ≥50% seizure reduction, including six (21%) with ≥80% seizure reduction. Additionally, one patient with idiopathic generalized epilepsy had a significant decrease in seizure frequency (percent not calculated) with 400 absence seizures/month at baseline. On the diet, she had a 1-h absence seizure each week.

Nine patients (31%) had no improvement or early diet discontinuation the diet. Three patients had a ≥50% increase in seizure frequency while on the diet, despite compliance and documentation of 4+ urinary ketones.

Table 1
Patient data.

16 women, 13 men		
Age: Mean 32 years (11–51 years)		
Epilepsy type:		
Idiopathic generalized		4
Focal epilepsy		11
Symptomatic generalized		14
Duration of diet:	Mean	
	9 months (0.13–35 months) 5 completed >23 months (24 months maximum duration recommended) 3 of these patients on modified Atkins diet after 24 months	
Efficacy		
Improvement: (52%)		15 patients
Overall improvement, % reduction unclear		1
(400 absence seizures/month baseline with daily seizures; on diet had prolonged absence seizure (1 h)/week)		
>50% reduction		13
Including:		
sz-free for 1 year (then difficulty with diet compliance)		1
sz-free for 3 weeks – unable to tolerate diet further		1
1 patient 135 absence sz/month, 8 GTC sz/mo baseline; then absence szs eliminated on diet, 5 GTC/month		1
40% reduction		1
>80% reduction		6
No improvement (31%)		9 patients
Initial improvement, then no improvement		2 patients
Unable to successfully initiate (7%)		2 patients
Increased (>50%) seizure frequency > 1 seizure type (10%)		3 patients
Reason for discontinuation		
Difficulty with compliance		11
Ineffective		9
Fatigue		1
Metabolic acidosis		1
Lost to follow-up after 4 months		1
Weight loss		1
Duration 2 years		5
Lipids:		
	Pre-diet (mean)	Diet discontinuation (mean)
Cholesterol	216 mg/dl (120–304, SD 50.8)	261 mg/dl (123–395, SD 65.2)	$p = 0.024$
Chol/HDL	4.4 (1.9–8.4, SD 1.8)	5.5 (1.9–10.4, SD 2.1)	$p = 0.005$
HDL	50.5 mg/dl (33–99, SD 19)	48.5 mg/dl (33–109, SD 20.4)	$p = 0.69$

Early response (within 3 weeks, usually seen during the initial hospitalization) was generally predictive of long-term response. For the three patients who remained on a modified high fat diet after full ketogenic diet discontinuation, two continued to experience a >50% reduction in seizure frequency. However, seizures increased in frequency after transition from the full ketogenic diet to the modified diet (in two patients >80% seizure reduction was reduced to >50% and <80% reduction; the other patient's seizure frequency reverted to baseline).

3.3. Response by seizure type

There was a trend ($p = 0.11$) toward patients with symptomatic generalized epilepsy having a greater seizure reduction. Sixty-four percent of individuals with symptomatic generalized epilepsy had a ≥50% seizure reduction, and 36% had ≥80% seizure reduction. For focal epilepsy, 28% had ≥50% seizure reduction, with 7% experiencing a ≥80% reduction.

3.4. Adverse reactions/complications

Sixteen patients reported adverse effects, and constipation and undesired weight loss (5 patients each) occurred most. See Table 1 for details. All adverse effects resolved after dietary modification or diet discontinuation.

3.5. Weight

Most individuals lost weight, an average of 7.98 kg (SD 10.6 kg). In the majority, patients had desired weight loss. In undesired weight loss (5 patients), caloric adjustments resulted in weight stabilization.

3.6. Reason for diet discontinuation

The two major reasons for diet discontinuation were difficulty in compliance (11 patients) and lack of efficacy (9 patients). See Table 1 for details. At 3 months, 62% of remained on the diet. This declined to 38% by 6 months.

3.7. Lipids

The majority of patients had an increase in total cholesterol and cholesterol/HDL ratio, but HDL tended to remain stable. See Table 1 for details.

3.8. Carnitine

Three patients had elevated triglyceride levels at the onset of the diet, which increased further with diet initiation. All three patients were treated with carnitine supplementation (990–1980 mg/day) with subsequent reduction in triglycerides (decreased from 248 to 161 mg/dl, 310 to 58 mg/dl, and 1071 to 271 mg/dl, respectively), with normalization of the carnitine.

3.9. Other laboratory data

Six of the earlier patients had reductions in serum selenium. These normalized with selenium supplementation. In later patients routine selenium supplementation began from the time of diet initiation, which prevented further selenium depletion.

3.10. EKG and cardiac data

No patient who was on the diet for a minimum of 6 months had any clinically significant EKG abnormality. One patient, who elected to continue the diet for 23 months, then continued on a modified high fat diet, had a normal persantine thallium cardiac stress test. As previously reported, one patient had a myocardial infarction five months after being on the diet for five months.[5]

4. Discussion

In this largely adult series of patients, approximately half had a significant reduction in seizure frequency. A favorable short-term response was generally predictive of long-term seizure control. The main reasons for diet discontinuation were difficulty with compliance and lack of efficacy. Patients with symptomatic generalized epilepsy remained on the diet the longest. In select individuals, continuing the diet beyond 24 months may provide benefit which might outweigh potential risks of the diet. A small number experienced more seizures, but it is unclear if this was directly related to the diet.

While the majority of patients continued the diet for at least 3 months, only a minority (38% of patients) remained on the diet for at least 6 months. The diet itself was generally well-tolerated. While the total cholesterol generally increased, the HDL remained relatively stable. This is in contrast to what has been reported in some children,[10] in whom HDL levels decreased. It is not clear whether this is represents an age-related difference. While the trend of lipid changes seen was unfavorable, it is not clear such changes would cause a significant increased risk of atherogenicity during the duration of the diet. As previously reported,[5] there was one patient with a myocardial infarction. However, this occurred in the setting of a known pre-existing dyslipidemia (cholesterol 304) after being on the diet for five months. Thus it is unclear that the diet contributed significantly toward increasing his risk for a myocardial infarction. However, after this patient, only patients with normal baseline lipid profiles were treated.

As in children, total carnitine often decreased while triglycerides increased. Carnitine supplementation in these cases resulted in a reduction in the triglyceride level. The mechanism by which this occurs is likely similar to that seen during hemodialysis.[11] Carnitine regulates mitochondrial free fatty acid transport, and l-carnitine supplementation may decrease the availability of free fatty acids for triglyceride synthesis.[12]

5. Conclusion

While the modified Atkins diet should be considered first-line dietary therapy, the ketogenic diet is an alternative treatment which is effective in this age group and may be particularly useful in symptomatic generalized epilepsy.

Conflict of interest statement

The authors declare that there are no known conflicts of interest.

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