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Improving compliance in adults with epilepsy on a modified Atkins diet: A randomized trial☆

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ABSTRACT

Purpose: To determine whether use of a ketogenic formula during the first month of the modified Atkins diet (MAD) in adults with drug-resistant epilepsy (DRE) improves seizure reduction and compliance compared to MAD alone.

Methods: Eighty adults (age ≥18 years) with DRE and ≥4 reliably quantifiable seizures/month were enrolled. All participants were trained to follow a 20 g/day net carbohydrate limit MAD. Patients were randomized to receive one 8-ounce (237 mL) tetrapak of KetoCal®, a 4:1 ketogenic ratio formula, daily in combination with MAD during the first month (treatment arm) or second month (control/cross-over arm). Patients recorded urine ketones, weight, and seizure frequency and followed up at 1 and 2 months.

Results: By 1 month, 84% of patients achieved ketosis (median of 4–4.5 days). At 1 month, the treatment arm had a significantly higher ketogenic ratio and more patients with a ≥1:1 ketogenic ratio compared to the control arm. There was no difference in median seizure frequency, proportion of responders (≥50% seizure reduction), or median seizure reduction from baseline between groups. However, patients treated with KetoCal® during the first month were significantly more likely to continue MAD for 6 months or more.

Conclusion: Although supplementing MAD with a ketogenic formula in the first month did not increase the likelihood of reducing seizures compared to MAD alone, significantly more adults remained on MAD long-term with this approach. This suggests a potential strategy for encouraging compliance with MAD in adults with DRE.

1. Introduction

The modified Atkins diet (MAD) has been effectively used in children and adults with drug-resistant epilepsy (DRE) for almost two decades [1–7], however long-term compliance remains a major challenge to successful implementation [8,9]. KetoCal® is a ready-to-drink 4:1 ratio (fat: carbohydrates and protein in grams) nutritionally complete liquid formula that can be used as a meal substitute or supplement. A 2011 prospective study of 30 children with intractable epilepsy treated with MAD in combination with daily KetoCal® (powder mixed with water or used as a baking mix) found that children tolerated KetoCal® and that there was a > 50% seizure reduction in 80% of participants after 1 month [10], which is on average over 30% greater than rates reported previously for MAD alone in pediatric populations [11–14]. While some pediatric ketogenic diet centers routinely recommend that all children starting MAD also use KetoCal® during the initial month as a result, it remains unclear if a similar benefit would also be seen in adults. We hypothesized that including daily KetoCal® during the initial month of MAD would lead to greater seizure reduction over the MAD alone in adults with DRE. We also determined whether KetoCal® supplementation would lead to an improvement in compliance rates and diet adherence, reduced constipation, and improved tolerability and ease of use of MAD as secondary outcome measures.

☆ Statistical Analysis conducted by Dr. Tanya J. W. McDonald, MD, PhD, Johns Hopkins University School of Medicine.

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2. Methods

A randomized, open-label, non-blinded, prospective single-center study was conducted to determine whether KetoCal® use during the first month of MAD in adults with DRE improves seizure reduction and diet compliance compared to MAD alone. These questions meet Class II level of evidence. The study was approved by the Johns Hopkins Institutional Review Board and reported in ClinicalTrials.gov (NCT01834482). Written informed consent was obtained from all patients or a legally authorized representative.

2.1. Study participants and design

Consecutive adults with epilepsy seen in the Johns Hopkins Adult Epilepsy Diet Center (AEDC) from March 1, 2013 through September 30, 2017 were screened for eligibility.

2.1.1. Inclusion criteria

Inclusion criteria included age ≥ 18 years, the presence of at least 4 reliably quantifiable seizures per month, and failed trial of ≥ 2 anti-seizure drugs (ASDs) at maximum doses, appropriate for their seizure type(s).

2.1.2. Exclusion criteria

Patients who were unwilling to restrict carbohydrates, underweight (body mass index (BMI) ≤18.5), pregnant, had a history of kidney disease, hypercholesterolemia (> 300 mg/dl) or hypertriglyceridemia (> 200 mg/dl), milk allergy, a metabolic/mitochondrial disorder in which ketogenic diets are contraindicated, or prior use of MAD for ≥2 days, KetoCal® at any time, or the classic ketogenic diet within the past year were excluded.

Based on prior seizure efficacy studies in adults suggesting a 27% responder rate (≥50% seizure reduction) of MAD alone [5] and a hypothesis that KetoCal® supplementation would double the responder rate at 1 month to at least 60% [10], a minimum of 68 adults (34 in each arm) were needed to ensure statistical significance with 80% power. Prior published studies of MAD use in adults demonstrated study retention rates of 75% (6 out of 8 participants) [3], 87% (26 out of 30 participants) [2], and 84% (21 out of 25 participants) [5] at 1 month and 94% (17 out of 18 participants) [4] at 3 months based on the proportion of patients remaining in the study compared to initial enrollment (regardless of whether patients actually started MAD therapy). Thus, we anticipated an 85% retention rate at 1 month and targeted 80 adults (40 in each arm) for enrollment.

All eighty patients meeting criteria were instructed to follow a 20 g/day net carbohydrate limit MAD [7], and randomized using a random number generator to treatment (MAD and KetoCal® during 1st month, MAD alone during 2nd month) or control (MAD alone during 1st month, MAD and KetoCal® during 2nd month) arms (Fig. 1). Daily KetoCal® liquid tetrapak use was not blinded as there were no placebo liquids available with comparable taste and consistency. One 8-ounce (237 mL) tetrapak provided 356 calories, 7.32 g of protein, 4.1 g of carbohydrates, 1.45 g of net carbohydrates (net = total carbohydrates – fiber), and 35.1 g of fat. Patients were limited to one tetrapak per day during the month of KetoCal® use. After the end of the study at 2-month follow-up, patients were allowed to continue/re-start KetoCal® as desired off-study, with follow-up offered and, if available, clinical data was collected at 6 months. For those patients who continued MAD use beyond the 2-month study period, we conducted an assessment of continued diet therapy and total diet duration for all study patients on September 30, 2017, which allowed for a minimum of 6 months of follow-up per patient.

2.2. Diet analysis and clinical data

Participants self-reported diet intake with 3-day food records at baseline, 1 and 2 months. Food records were analyzed using Nutrition Data System for Research software [15]. Diet adherence was defined by patient self-report of continued MAD use. A monthly calendar was provided to record urine ketones daily until ketosis (defined as ≥40 mg/dl or moderate) then biweekly, weight weekly, and seizures daily. Urinalysis and serum beta-hydroxybutyrate level (goal 2–4 mmol/L) were assessed at follow-up. Achievement of ketosis was defined by reaching either moderate urine ketones or a beta-hydroxybutyrate level ≥ 2 mmol/L by 2 months. Fasting serum cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured at baseline and follow-up visits. Participants were asked to rate the convenience, taste, texture, and tolerance level of MAD and KetoCal® using a 10-point scale (with 1 = poor and 10 = excellent).

2.3. Statistical analyses

Continuous variables were expressed as means (standard deviation) or medians (interquartile range) and categorical variables as counts (percentage). Differences between groups, at baseline and follow-up, were assessed using Fisher's Exact test for categorical variables and the student's *t*-test for unpaired data or the nonparametric Mann Whitney *U* test, as appropriate based on normality of distribution ($p < 0.05$). Repeated measures of weight were assessed using ANOVA and repeated measures of seizure frequency and lipid levels were assessed using the nonparametric Related-Samples Friedman's Two-Way ANOVA with post-hoc Wilcoxon Signed Rank Tests with Bonferroni adjustment for pairwise comparisons. To adjust for potential confounders, a binary logistic regression model was used to examine the association of any identified demographic and clinical variables that differed between groups at baseline with the primary outcome (responder rate) and secondary outcomes (overall MAD compliance rate, diet adherence at specific time points, achievement of ketosis, and constipation rate). Separate regression models were fitted for each end-point. All statistical analyses were performed using IBM SPSS Statistics version 25.

3. Results

3.1. Baseline demographic and clinical data

Two-hundred and thirty-four consecutive patients were screened for study enrollment. Of these, 154 were excluded and the remaining 80 participants were randomized (Fig. 1). There was no statistically significant difference between groups based on age, gender, epilepsy type, duration of epilepsy, vagus nerve stimulation use, number of ASDs used prior to study onset, or median baseline seizure frequency (Table 1). However, at baseline, patients in the treatment arm had significantly lower weight ($t(78) = 0.020$, $p = 0.039$, 95% confidence interval [CI] +1.2 to +44.9) and body mass index ($t(78) = 2.438$, $p = 0.007$, 95% CI +1.2 to +7.5) compared to controls (Table 1).

3.2. Seizure outcome

Following randomization, six patients elected not to start MAD, five patients were lost to follow-up by 1 month, three patients stopped or did not adhere to MAD consistently, and four patients had less than 3 weeks of KetoCal® use during the assigned month (deemed non-compliant with KetoCal®). An additional six patients were excluded from seizure efficacy analysis at 1, 2 and 6 months (Fig. 1) as two patients did not record daily seizures and four patients changed ASDs during the 2-month study period. The effect of KetoCal® on seizure frequency was measured by comparing 1-month responder rates, median seizure frequency/week, and median percent seizure reduction from baseline between treatment (n = 31) and control (n = 25) arms in the study. While there was no significant difference between groups for these measures at 1, 2 or 6 months of follow-up, both groups had over