Current Literature
In Clinical Science

Ketogenic Diet: It Has a Role in Our Armamentarium of Treatment of Refractory Seizures

Phase I/II Multicenter Ketogenic Diet Study for Adult Superrefractory Status Epilepticus.

Cervenka MC, Hocker S, Koenig M, Bar B, Henry-Barron B, Kossoff EH, Hartman AL, Probasco JC, Benavides DR, Venkatesan A, Hagen EC, Dittrich D, Stern T, Radzik B, Depew M, Caserta F M, Nyquist P, Kaplan PW, Geocadin RG. *Neurology* 2017;88:938–943.

OBJECTIVE: To investigate the feasibility, safety, and efficacy of a ketogenic diet (KD) for superrefractory status epilepticus (SRSE) in adults. METHODS: We performed a prospective multicenter study of patients 18 to 80 years of age with SRSE treated with a KD treatment algorithm. The primary outcome measure was significant urine and serum ketone body production as a biomarker of feasibility. Secondary measures included resolution of SRSE, disposition at discharge, KD-related side effects, and long-term outcomes. RESULTS: Twenty-four adults were screened for participation at 5 medical centers, and 15 were enrolled and treated with a classic KD via gastrostomy tube for SRSE. Median age was 47 years (interquartile range [IQR] 30 years), and 5 (33%) were male. Median number of antiseizure drugs used before KD was 8 (IQR 7), and median duration of SRSE before KD initiation was 10 days (IQR 7 days). KD treatment delays resulted from intravenous propofol use, ileus, and initial care received at a nonparticipating center. All patients achieved ketosis in a median of 2 days (IQR 1 day) on KD. Fourteen patients completed KD treatment, and SRSE resolved in 11 (79%; 73% of all patients enrolled). Side effects included metabolic acidosis, hyperlipidemia, constipation, hypoglycemia, hyponatremia, and weight loss. Five patients (33%) ultimately died. CONCLUSIONS: KD is feasible in adults with SRSE and may be safe and effective. Comparative safety and efficacy must be established with randomized placebo-controlled trials. CLASSIFICATION OF EVIDENCE: This study provides Class IV evidence that in adults with SRSE, a KD is effective in inducing ketosis.

A Randomized Controlled Trial of the Ketogenic Diet in Refractory Childhood Epilepsy.

Lambrechts DAJE, de Kinderen RJA, Vles JSH, de Louw AJA, Aldenkamp AP, Majoie HJM. *Acta Neurol Scand* 2017;135:231–239.

OBJECTIVE: To evaluate the efficacy and tolerability of the ketogenic diet (KD) during the first 4 months of a randomized controlled trial (RCT) in refractory epilepsy patients aged 1–18 years. METHODS: Children and adolescents with refractory epilepsy, not eligible for epilepsy surgery, were included. Following 1 month at baseline, patients were randomized to either the KD or to care as usual (CAU). Primary outcome is the proportion of patients with at least 50% reduction in seizure frequency at 4 months. Secondary outcomes are mean percentage of baseline seizures, seizure severity, and side effects. RESULTS: Fifty-seven patients were randomized; nine dropped out, leaving 48 for analysis (i.e., 26 KD, 22 CAU). In an intention-to-treat analysis, 13 patients (50%) treated with the KD and four patients (18.2%) of the CAU group were responders. Mean seizure frequency at 4 months compared to baseline, after removal of two outliers in the KD group, was significantly lower (P = 0.024) in the KD group (56%) (95% CI: 36–76) than in the CAU group (99%) (95% CI: 65–133%). Twice as many patients in the KD group had a relevant decrease in seizure severity score (P = 0.070). Patients treated with the KD had a significantly higher score for gastrointestinal symptoms (P = 0.021) without an increase in the total score of side effects. CONCLUSIONS: This trial provides class I evidence that the KD is an effective therapy in children and adolescents with refractory epilepsy compared with CAU. Most often reported side effects are gastrointestinal symptoms. The study has been registered with the Netherlands Trial Registry (NTR2498).

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Commentary

Despite there being over 20 FDA-approved antiepileptic drugs (AEDs), approximately one-third of patients with epilepsy continue to have seizures. Ongoing seizures, particularly in vulnerable populations, such as children and those with re-

fractory status epilepticus, are associated with significant risks including death. As many of the available AEDs have common mechanisms of action (e.g., sodium channel blockade) it is important to explore the feasibility and effectiveness of other treatments, such as dietary therapy. Dietary therapy including the ketogenic diet (KD) is a nonpharmacologic treatment for epilepsy, notably drug resistant epilepsy. Historically, the effects of fasting on seizure cessation were noted and the concept of the KD, typically a 4:1 ratio of fat to protein and carbohydrate combined, was first studied and developed in the 1920's. Since the 1970s, the diet has gained an increasing role in our treatment of refractory seizures but despite its long history, few controlled studies are available. The first randomized controlled trial was done in 2008 in children aged 2 to 16 years who had at least daily seizures and had failed to respond to at least two AEDs (1). The investigators found significantly lower seizure frequencies in children treated with the KD when compared with a control group. Another randomized trial compared the classic 4:1 KD with a medium-chain triglyceride (MCT) diet and found comparable efficacy and tolerability among children with intractable epilepsy (2). Further study is necessary and important to increase our understanding of dietary therapies and their place in our armamentarium of treatment of patients with refractory epilepsy. Two recent controlled studies aimed to further investigate the role of the KD in different populations, one in children with refractory epilepsy and one in adults with superrefractory status epilepticus.

Lambrechts and colleagues evaluated efficacy and tolerability of the ketogenic diet among children with refractory childhood epilepsy. Children and adolescents with refractory epilepsy (seizures not adequately controlled by ≥ 2 AEDs) aged between 1 and 18 years at a tertiary referral center for epilepsy in the Netherlands were included. After an initial 1-month baseline period, 57 subjects were randomized to either the KD or care as usual (CAU). Because of the previously discussed reported similar efficacy between the KD and MCT diet, most subjects with the exception of those who received only tube feeding were given the MCT diet. The primary outcome was proportion of subjects with at least 50% reduction in seizure frequency. In an intention to treat analysis, 50% treated with the KD for 4 months were responders, three of whom were seizure free and the other three had greater than 90% seizure reduction compared with 18% of the CAU group of whom two were seizure free and one had greater than 90% seizure reduction. The investigators also evaluated seizure severity scales, an uncommon practice in clinical epilepsy trials. Similar to the responder rates, the proportion of patients with a relevant decrease of the seizure severity score was threefold higher in the KD-treated group at 6 weeks and 2-fold higher at 4 months Overall, there was no difference in side effects between the two groups. More specifically, there was a significant difference in gastrointestinal side effects with the KD group having a higher score at 6 weeks and at 4 months.

Superrefractory status epilepticus (SRSE) is defined as refractory status epilepticus that returns after intravenous anesthetic agents are withdrawn. SRSE is associated with a high risk of morbidity and mortality and treatment options are limited. Similar to treating children with refractory seizures, therapies beyond AEDs and anesthetics need to be explored. Retrospective studies demonstrate that the KD may have potential efficacy in treatment of patients with SRSE (7-9). In order to investigate further, Cervenka and colleagues performed a prospective, multicenter, open-label study investigating feasibility, safety, and efficacy of KD for patients 18 to 80 years of age with SRSE. Over a 15-month period, 24 adults were screened at five medical centers and 15 were enrolled and treated with a classic 4:1 ratio KD. Patients had a median age of 47 and had varied etiologies. The primary outcome was feasibility. Secondary outcomes included adverse and serious adverse events and response to treatment. Eleven of 14 patients who completed the study had resolution of SRSE in median of 5 days. Five patients died – one had care withdrawn; three never had SRSE resolution; and one had KD stopped after SRSE resolution, but later had a pulseless electrical activity cardiac arrest thought to be unrelated to KD. Six of 11 patients who achieved resolution of SRSE were transitioned to a modified Atkins diet and four remained on it at most recent follow-up. This study finds that KD initiation was possible in patients with SRSE and the majority of patients studied (73% in intention to treat analysis) had resolution of SRSE.

Although these studies support potential efficacy of KD in different populations of patients with refractory seizures, they provide no insight into potential mechanisms to explain anti-epileptogenic properties of the KD. The exact mechanisms by which the KD is antiepileptic is unknown. The effects of ketones and glucose restriction likely act though multiple mechanisms and interactions with receptors, channels, and metabolic enzymes (10).

Results from these studies provide class I evidence (RCT of KD in refractory pediatric epilepsy) and class IV evidence (open-label study of KD in SRSE) of KD in clinical practice. Although the study in children and adolescents is a randomized controlled study, it is open label and relies on parental reporting both of seizure frequency and severity. When considering an option like the KD, parents are typically highly motivated and may be influenced by reporting bias. The generalizability of findings to a larger population of children and adolescents with refractory seizures is difficult as it is important to recognize that with the exception of tube fed children, KD initiation and implementation is not always practical, particularly in adolescents. Other recent studies in adolescents and adults have focused on a low glycemic diet or Modified Atkins diet as these diets are typically easier to implement and better tolerated. As for the study of patients with SRSE, its findings are limited because as with all therapies, randomized placebo controlled studies are needed to fully determine if KD is safe and effective among patients with SRSE. This study raises the question of whether a well-designed adequately powered randomized controlled study in this population can be done; it took 15 months to enroll 15 subjects at five medical centers. These patients are often metabolically unstable and the KD diet is not always practical. Given the promising results in the selective group studied in this open-label study, there are potential ethical concerns about giving a placebo to appropriate SRSE patients as this condition is associated with high mortality rates.

Overall, the results of these studies suggest that the KD should be considered for pediatric patients with refractory epilepsy and patients with SRSE for whom there are so few options. Practical limitations, potential bias reporting, and lack of adequate randomized controlled studies do however, limit generalizability and significance of findings.

by Alison M. Pack, MD, MPH

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