

Ketogenic diet for treatment of epilepsy

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ABSTRACT

QUESTION Families of children with epilepsy now ask about the ketogenic diet at clinic visits. Is it effective and safe to use for treatment of epilepsy?

ANSWER The ketogenic diet can be considered an option for children with intractable epilepsy who use multiple antiepileptic drugs. It is a treatment of choice for seizures associated with glucose transporter protein deficiency syndrome (ie, De Vivo disease) and pyruvate dehydrogenase complex deficiency. The diet's strictness, unpalatability, and side effects limit its use, adversely affecting patients' compliance and clinical efficacy.

RÉSUMÉ

QUESTION Les parents d'enfants souffrant d'épilepsie nous posent maintenant des questions au sujet des régimes cétogènes lors de leurs visites en clinique. Sont-ils efficaces et sûrs dans le traitement de l'épilepsie?

RÉPONSE Un régime cétogène peut être envisagé comme une option pour les enfants atteints d'épilepsie réfractaire qui utilisent de multiples médicaments contre l'épilepsie. C'est un traitement de première intention dans les cas d'épisodes associés au syndrome du déficit de la protéine transporteuse de glucose (p. ex. maladie de De Vivo) et au déficit en complexe pyruvate-déshydrogénase. Le caractère strict de ce régime, son manque de saveur et ses effets secondaires en limitent l'utilisation, et nuisent à l'observance par les patients et à l'efficacité clinique.

The ketogenic diet, initially described by Hugh Conklin, a Michigan pediatrician, is a high-fat, low-carbohydrate, and normal-protein diet that has been used for the treatment of medically refractory childhood epilepsy since the 1920s.¹ Although its use became less frequent with the introduction of anticonvulsant medications, the diet has regained recognition over the past 15 to 20 years. Medical associations have not been enthusiastic to develop guidelines and to endorse the diet. As a result, clinical centres follow different protocols, making comparisons and evaluation of the diet's efficacy difficult.

Description

The ketogenic diet includes 80% fat, 15% protein, and 5% carbohydrate; the ratio of fat to carbohydrate plus protein ranges from 2:1 to 4:1, with higher ratios seen as more restrictive but more effective.^{2,3} Most of the fat in the classic, most commonly used ketogenic diet is provided as long-chain triglycerides. A variant of the classic ketogenic diet is the medium-chain triglyceride diet, which was introduced in an attempt to improve its palatability by allowing more carbohydrates yet preserving ketosis. Although it can be more ketogenic, it is less used, as it often causes gastrointestinal side effects. Several infant formulas are also available.

The ketogenic diet predisposes to nutritional deficits in energy, proteins, minerals, and vitamins and excess in

lipids, saturated fat, and cholesterol. Use of such an unbalanced diet requires particular attention to implementation and monitoring, particularly in children. Strict adherence to the dietary plan is required, and even small amounts of food beyond the diet or deviation in food preparation might cause considerable reduction in the efficacy of the diet.

Initiation of the ketogenic diet is preceded by a 24- to 48-hour fast, with the patient being hospitalized. During the fast, the patient can drink water or sugar-free beverages and can eat unsweetened gelatin. Alternatively, Bergqvist et al have shown that a gradual initiation results in fewer adverse events and is overall better tolerated yet maintains the efficacy of the diet.⁴ Contraindications such as β -oxidation defects, liver disease, or metabolic disease interfering with glucose or ketone homeostasis must be excluded before initiation of the diet. Laboratory parameters of blood and urine glucose and ketones need to be monitored during fasting. The diet is introduced by starting with one-third of calories per meal, increasing to two-thirds of calories per meal and to the total amount of calories per meal every 24 hours. Patients are discharged when the total amount of calories per meal is reached and well tolerated, typically 2 to 3 days after initiation of the diet. Parents, patients, and caretakers are educated during admission about suitable food items, calculation, and preparation of ketogenic meals. If the diet is initiated without hospitalization, adequate facilities must be available to instruct families on meal preparation and monitoring techniques.



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Meal plans are patient-tailored and can include heavy cream, bacon, eggs, tuna, shrimp, vegetables, mayonnaise, sausages, and other high-fat and low-carbohydrate products. Patients are not allowed starchy fruits or vegetables; breads, pasta, or grains; or sources of simple sugars. The food preparation can be onerous for parents and patients, who must pay great attention to selecting, weighing, and cooking every meal or dietary component. While on the diet, patients should also receive recommended daily intakes of vitamins and minerals (in sugar-free formulations), as well as calcium supplementation. Precise quantities of foods for the diet and meal plans are derived using individual patient data (age, weight, etc) in computer applications such as the KetoCalculator.⁵ At least 1 g of protein per kg of body-weight should be supplied daily to children older than 3 years of age (and more to younger children) to preserve growth.

Children on the diet need to be seen monthly by registered dietitians, with adjustments to diet according to each child's needs to allow for normal growth and weight gain.

Mechanism of action

Despite nearly a century of use, the mechanisms underlying the clinical efficacy of the ketogenic diet remain unknown. Several mechanistic theories of chronic ketosis action have been proposed, including modification of the tricarboxylic acid cycle to increase γ -aminobutyric acid synthesis in the brain, limit reactive oxygen species generation, and boost energy production in brain tissue.⁶ As a result, hyperpolarization of neurons occurs, stabilizing synaptic function and increasing resistance to seizures throughout the brain.

Based on the tricarboxylic acid mechanism, the ketogenic diet is an appropriate first-line therapy for patients with seizures associated with metabolic disorders such as glucose transporter protein deficiency (ie, De Vivo disease) and pyruvate dehydrogenase complex deficiency.⁷ Another indication for the ketogenic diet is intractable childhood epilepsy.

Clinical trials

In a recent Cochrane systematic review of the evidence regarding the effects of ketogenic diets, Levy and Cooper found no randomized controlled trials (RCTs).⁸ Another literature review of published data between the 1920s and 2003 concerning the efficacy of the ketogenic diet, including 20 retrospective and prospective studies, concluded that the diet appears to be a very effective treatment for epilepsy, particularly in childhood.⁹

A meta-analysis of the efficacy of the ketogenic diet for epilepsy that included 19 observational studies with 1084 patients with a mean(SD) age of 5.8(3.4) years found that the pooled odds ratio of treatment success, defined as a greater than 50% seizure reduction, among patients staying on the diet relative to those discontinuing the diet was 2.25 (95% confidence interval, 1.69 to 2.98).¹⁰

A recently published RCT showed the efficacy of the ketogenic diet in children.¹¹ Neal et al demonstrated in an RCT of 145 children, aged 2 to 16 years old who had at least daily seizures and had failed to respond to at least 2 antiepileptic drugs for 3 months, that the mean percentage of baseline seizures was significantly lower in the diet group than in the control group (62% vs 137%, 75% decrease, $P < .0001$).¹¹ Twenty-eight children (38%) in the diet group had greater than 50% seizure reductions compared with 4 (6%) controls ($P < .0001$), and 5 children (7%) in the diet group had greater than 90% seizure reductions compared with no controls ($P = .058$). In another RCT, Neal et al found, in 149 children with intractable epilepsy, that both classical and medium-chain triglyceride ketogenic diet protocols are comparable in efficacy and tolerability and that both ways of implementing the diet have their place in the treatment of childhood epilepsy.¹²

As for adults, a prospective study of 9 adult patients with a mean (SD) age of 28(6) years demonstrated extremely low adherence; only 2 subjects concluded the study owing to an early mean (SD) dropout at 8 (2) weeks.¹³ However, 2 patients who completed 12 weeks of treatment had more than 50% reductions in the frequency of their seizures.¹³

Benefits and side effects

Patients on the diet become more alert and exhibit considerable improvements in attention, comprehension, activity levels, and endurance.⁷ Most of the side effects from the ketogenic diet are related to energy and nutrient deficiencies. Lack of protein, carbohydrates, and other nutrients can result in lack of weight gain and growth inhibition, especially at a young age. Inadequate calcium intake can further impair bone mineralization in children already at risk of osteopenia due to antiseizure therapy. Lack of fibre in the diet causes constipation. Acidosis is also commonly observed. Less common are kidney stones and hyperlipidemia.¹⁴ Adjustments to the diet (eg, increased protein and polyunsaturated fat) can be made in children with high lipid concentrations. Serious adverse events include coma and obtundation.⁷ Rare side effects include cardiomyopathy, prolonged QT syndrome, vitamin and mineral deficiencies, pancreatitis, basal ganglia injury, and bruising.¹⁵ The long-term results of these side effects have not been adequately studied.

Regular admissions and easy access to appropriate health care providers are needed for follow-up and for monitoring side effects. Laboratory tests for electrolytes, liver function, plasma lipid profile, proteins, and complete blood count are periodically performed. Anthropometry (weight, height, skinfold thickness) should be assessed at each visit and growth should be monitored using growth charts. Routine examinations of bone mineral density or bone enzymes are required. Typically children are kept on the diet for 1 to 2 years as long as it is beneficial and side effects are tolerable. The diet is tapered over several months by lowering the ratio of fat to protein plus carbohydrate, then slowly relaxing restrictions on weighing foods and measuring carbohydrate intake.


Controversies

Several controversial and largely unanswered issues remain about the ketogenic diet, such as the necessity of the initial fast, duration of the diet, fluid restriction, the use of medium-chain versus long-chain triglyceride fatty acid foods in the diet, the need for carnitine supplements, and potential long-term adverse effects of the diet and its interactions with antiseizure drugs. An international expert panel could help clarify those concerns.

Another issue is the patients' compliance. Less than half of the patients remain on the diet for more than 1 year.¹⁶ The reasons for diet discontinuation include a lack or loss of efficacy (67%), adverse events (12%), caregivers' issues, and patients' unwillingness to continue on the diet (25%).¹⁷ Ingestion of additional "forbidden foods" is a common cause for an insufficient level of ketosis.

Conclusion

The ketogenic diet can be considered as an option for children with intractable epilepsy who use multiple

antiepileptic drugs, and is a treatment of choice for seizures associated with glucose transporter protein deficiency (ie, De Vivo disease) and pyruvate dehydrogenase complex deficiency. The diet's strictness, unpalatability, and side effects limit its use and adversely affect both patients' compliance and clinical efficacy. 

Competing interests

None declared

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