

Dietary Treatment for Patients With Epilepsy

Ketogenic diets are an effective treatment when used properly with medical supervision and support.

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Introduction

Dietary treatments of epilepsy have their origin in periodic fasting and water diets, both ancient seizure remedies. Known across cultures to stop seizures and prescribed by Hippocrates, fasting is the oldest recorded treatment of epilepsy.¹ The most famous historical description is in the Bible story (Mark 9:29), in which a boy is cured of seizures by “fasting and praying.” Cyclic fasting was the major treatment for people with epilepsy before the development of antiepileptic medications (AEDs).² Adherence to fasting was a major issue because most people would rather eat and have seizures than starve. Research investigating

metabolic shifts associated with fasting led to the creation of what is now termed the *classic ketogenic diet* (CKD) in 1921.³ Through manipulation of macronutrient ratios (fats, proteins and carbohydrates), the CKD mimics metabolic changes seen with fasting: slowed glycolysis, suppression of insulin secretion, upregulation of gluconeogenesis, and induction of fatty oxidation with increased production of ATP and high levels of ketone bodies (Figure 1). In current ketogenic diet (KD) treatments for epilepsy (CKD, gradual KD, medium chain triglyceride (MCT) KD, modified Atkins, modified KDs, and low-glycemic index treatment) what varies is how strongly the major metabolic pathways are induced or by the ratio of fat to combined protein and carbohydrate composition.

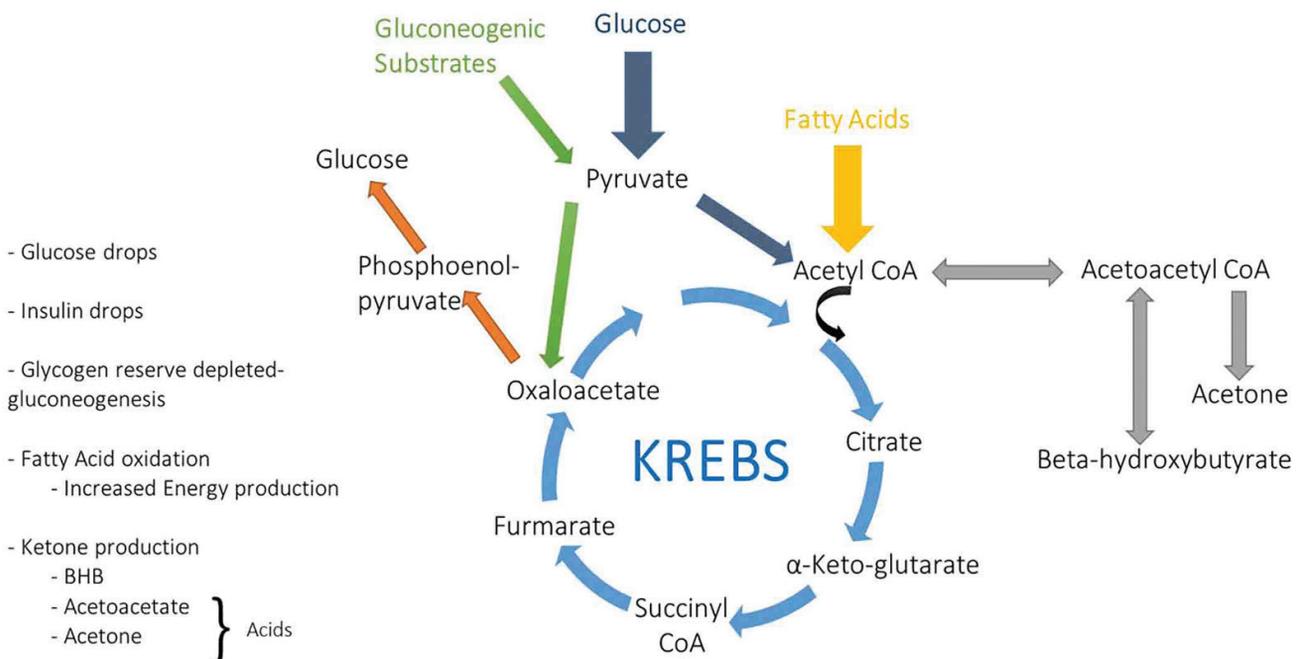


Figure 1. Metabolic changes with fasting and ketogenic diets.

Ketogenic Diets

The average adult in the US eats a diet containing 2,200 kcal per day composed of approximately 55% carbohydrates, 30% fat, and 15% protein. Carbohydrates and protein provide 4 kcal/gram and fat generates more than twice that, 9 kcal/gram. In a KD, meals are higher in fat and thus smaller compared to typical meals.

Classic Ketogenic Diet

The CKD is 90% fats, 7% proteins, and 3% carbohydrates. Ratios are useful in discussing these diets that are typically composed of a 4:1 ratio of grams of fat: grams of protein and carbohydrates combined. Lower ratios are sometimes prescribed and used to meet protein requirements for adolescents and adults. For infants, a 3:1 ratio is recommended as the initial starting point, to meet protein needs,⁴ although higher ratios can be used if needed. Calorie and macronutrient composition of each meal is precisely calculated and weighed on a gram scale for the duration of treatment (Table 1). Vitamins and minerals in the typical diet are primarily present in carbohydrates (vegetables, fruits, and grains) and proteins (meat, fish, egg, plants). Patients prescribed KD therefore must take vitamin supplements to be nutritionally complete.⁵

Typically, CKD was started in the hospital and used to be preceded by a several-day fast, until 10% weight loss and brisk ketosis was observed. Pretreatment fasting has since been abolished as studies show it is not needed for efficacy and more than doubles side effects and the need for interventions.⁶ Centers treating patients with KD now use gradual protocols in which dietary fat composition is gradually increased (Table 2).⁷

Initiation of treatment in the inpatient setting is used

	Fat	Carbohydrate	Protein
	% daily calories		
Typical US diet	20-30	50-55	15-20
CKD 4:1	90	3	7
MCTKD oil diet 4:1 30% to 60% MCT oil	73	17	10
MKD <2:1 modified Atkins diet	60-70	3-10	20-40
Low-glycemic-index diet	60-70	10 ^a	20-30

a: in low-glycemic-index diet, all carbohydrates have a glycemic index < 50.
Abbreviations: CKD, classic ketogenic diet; KD, ketogenic diet; MCT, medium-chain triglyceride, MKD modified ketogenic diet.

when transitioning a patient to a 90% fat diet quickly, over 3 to 5 days. The inpatient setting allows for direct observation, prevention and treatment of common side effects (eg, hypoglycemia and acidosis, lethargy, vomiting), and concentrated patient and caretaker education by the KD team (eg, weighing food, calculations, cooking, and handling sick days on an almost all-fat diet). Outpatient protocols (eg, those used in Canada, England, and the Netherlands) require a slower KD advancement over several weeks to be safe. Transition into ketosis is not observed and interventions may therefore be delayed. Communication must be established via phone and email. Frequent visits for teaching and monitoring are also necessary, which can be difficult for families living at a distance. However, the patient is able to start the KD in the comfort of home.⁸

Modified Ketogenic Diets

The CKD is precise and structured, with all meal ingredients weighed to ensure appropriate and exact composition; no extra food is permitted. The CKD may be too restrictive for some patients. In the early 2000s, more relaxed versions (eg, the lower-ratio modified KD) were developed including the modified Atkins diet, modified ketogenic diets, and the low-glycemic-index diet. These diets also restrict carbohydrates tightly—often to 10 to 20 gram per day—but do not require use of a scale. Instead net carbohydrates and calories on food labels are counted. Protein is considered *unlimited* and fat *encouraged*. Of these modified diets, the low-glycemic-index diet allows for the most carbohydrates—10% of calories (often 40-60 grams carbohydrates/day)—although carbohydrates must be low in glycemic index (< 50).⁹

Mechanisms of Action

Although the CKD is almost 100 years old, the precise mechanisms of action by which dietary treatments stop seizures are not yet known. Not surprisingly, recent in vivo and in vitro studies reflect that a diet with complex effects on human metabolism has multiple complex mechanisms of action. Clinical effects are short, medium, and long term. Short term, seizures can stop in some individuals as soon as they become ketotic. Continued reduction in seizures occurs over the medium term, and in the long term, it is possible to stop the diet without seizure recurrence, suggesting the diet is antiepileptogenic, not just anticonvulsant.

Mechanisms considered to be likely contributors to anticonvulsant effects include high levels of ketone bodies,¹⁰ indirect effects of increased ATP production and adenosine,¹¹ increased GABA synthesis and reduced presynaptic glutamate,¹² changes in neural ATP-sensitive potassium-channel activation,¹³ dampened neural activity through increased autocrine regulation, inhibition of histone deacetylases, hydroxycarboxylic acid receptor 2 (HCA2) and nucle-

TABLE 2. COMPARING FASTING TO GRADUAL KETOGENIC DIET INITIATION PROTOCOLS

Nutrient Ratios		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Fat: Protein + Carb	Fasting	0	0	4:1	4:1	4:1	4:1
	Gradual	Regular Food	1:1	2:1	3:1	4:1	4:1
% Kcal/d	Fasting	0	0	1/3	2/3	100%	100%
	Gradual	100%	100%	100%	100%	100%	100%

Note: Condensed 4-day gradual protocol used at the Children's Hospital of Philadelphia as of 2018 is within the dark-black box. Abbreviations. Carb, carbohydrates; d, day; Kcal, kilocalories

otide-binding domain, leucine-rich-containing family, pyrin domain-containing-3 (NLRP3) inflammasome,¹⁴ changes in the mechanistic target of rapamycin (mTOR) (a phosphatidylinositol 3-kinase [PI3K]-related kinase involved in cell cycle regulation) pathway,¹⁵ and changes in the gut microbiome.¹⁶

Not for Self-Administration

Doing what popular culture has termed *keto* became popularized by the weight loss industry when Atkins published his book. Many other fields are now looking into potential benefits. Athletes like long distance runners and body builders use the diet to alter body composition, burn fat, and provide better energy during high-endurance races. The media has been flooded with cookbooks and videos for what is being sold as *do-it-yourself-keto*. The ketogenic diets that have proven effective for epilepsy are not the same as these milder do-it-yourself varieties. It cannot be emphasized enough that the **for a patient with epilepsy, guidance of a dietician is the absolute minimal requirement** to begin ketogenic diets safely, monitor side effects during treatment, and assist with adjusting and transitioning from a therapeutic ketogenic diet.

Successful larger centers often use family-centered team approaches with specially trained dietitians, nurses, and social workers.¹⁷ At our center, we have a *medical chef educator* on the team (Figure 2). This individual is responsible for creating meals that taste delicious, creating recipes, and arranging



Figure 2. Meals before (left) and after (right) having a medical chef educator on the team.

cooking classes where techniques are taught to patients and caregivers. Keeping meals that are 90% fat tasting delicious is the key to adherence and success with dietary therapy.

Efficacy and Adherence to Treatment

There has not been a successful randomized double-blind clinical trial assessing the effectiveness of the ketogenic diet. Blinding research participants and researchers to food is difficult. There are more data from 9 randomized clinical trials in children with more than 700 participants total as well as several meta-analyses. Although each study has differences in diet implementation, the general numbers accepted as seizure reduction at 3 months are: 50% to 75% of participants have $\geq 50\%$ reduction in seizures and 15% to 25% of participants are seizure free.⁷ In adults, KDs have not been widely used until recently because of concerns about palatability and adherence. With the increasing modifications available, KD use is increasing in adults. Lower-ratio diets are used more commonly due to improved palatability. Adherence, important to everyone who uses these treatments, is imperative in adults and the major reason for discontinuing the treatment early. In some studies, up to 50% of adults stopped KD treatments for that reason.¹⁸ For children, all meals are prepared and fed to the child by highly motivated parents, whereas for adults with epilepsy they not only have to eat the food but also have to prepare it for themselves for the duration of treatment. There are now some prepared foods available for purchase in grocery stores or on the internet for lower-ratio KDs. But for those on higher ratios, these Atkins or keto products available for weight loss may not provide high enough ketosis to reduce seizures significantly. Finally, alcohol is a carbohydrate and consumption must be limited, if allowed at all, while trying these diets. For some adult patients this is a significant barrier to treatment with KD.

Do the Ratios Really Matter?

With the development of the lower-ratio ketogenic diets, proponents have strongly advocated for their use and claimed the reduction of seizures is similar to that seen

with CKD.¹⁹ Although some authors have gone so far as to suggest that we should abolish the gradual initiation of CKD and instead use only modified KD as treatment for epilepsy,²⁰ current clinical and scientific research suggests that higher ratios reduce seizures faster and more effectively within 1 to 3 months of treatment than lower-ratio diets that require more time—often 3 to 6 months of treatment.^{21,22} Beginning with a high-ratio KD and reducing the ratio after a few months is an option, particularly if adherence becomes an issue.⁷

Choosing Among Ketogenic Diets

The family and patient's preferences are important factors when choosing a KD; however, there are other factors to consider. For patients having epileptic encephalopathies with frequent seizures (ie, many times a day or hour), gradual initiation of CKD is recommended in order to reduce seizures quickly. Patients already on a feeding tube benefit from pre-made formulas in ratios of 3:1 and 4:1. For adults and adolescents who require large amounts of protein and for whom adherence to the high-fat diet can be difficult and for patients with less frequent seizures modified KD can be tried first. For those who have difficulty with the less rigorous structure of modified KDs, changing to CKD at a lower 2:1 ratio where everything is weighed may improve adherence more quickly.

Metabolic Clearance Before Initiation

Any patient considering KD must first be cleared as able to metabolically handle fats. That means completing a metabolic screen consisting of lactate, pyruvate, plasma amino acids, urine organic acids, total and free carnitines, and acyl-carnitine esters. Starting KD in a patient with a fatty-acid disorder will result in hyperlipidemia and lack of ketone production with hypoglycemia, which in a worst-case scenario can result in death if the diet is not stopped. Contraindications include carnitine deficiencies; primary and palmitoyl-transferase 1 or 2 and translocase deficiencies; beta oxidation defects; short-, medium-, or long-chain acyl-CoA dehydrogenase deficiency; medium-chain 3-hydroxyacyl-co enzyme A deficiency; pyruvate carboxylase deficiencies; and porphyria which requires a high-carbohydrate diet. Mitochondrial disorders are more complex as patients with some mitochondrial disease benefit from KD (eg, pyruvate dehydrogenase complex disorders and some electron transport chain disorders), although others' mitochondrial disease is worsened by KD as some are highly dependent on glucose. In patients with mitochondrial disorders, KD should only be initiated under the careful guidance of both the mitochondrial disease and KD teams.^{7,23}

Treatment Period

We ask patients to stick to KD treatment for 3 months to determine effectiveness. This treatment period was initially chosen from drug trials. Patients who respond typically

begin to show seizure improvement early. In 1 study, 75% of patients who responded to CKD treatment began to show changes by 2 to 4 weeks and 95% had significant changes in seizures by 3 months.²⁴ Another study looking at seizure freedom found that becoming seizure free for > 28 days occurred as late as 18 months, but that most children who became seizure free had some recurrence, and only 30% of treated patients achieved permanent remission. Those that did have recurrence of seizures, however, still had reduced seizures overall.²⁵

The long-term treatment period in responders (ie, those with > 50% reduction at 3 months) is typically 2 years, followed by a 6- to 12-month weaning period. Shorter use has been effective in infantile spasms, where KD has been successfully discontinued after only 6 to 8 months²⁶ and in status epilepticus, where the diet was used just to stop status, not as a maintenance treatment.²⁷ Longer treatment periods are now common for centers with large populations of patients using KD, with some patients staying on a version of KD for as long as 10 to 20 years. These patients failed weaning from KD, had seizures return when they came out of ketosis, and had other KD-related benefits including improved cognition and attention and reduced medication use. In fact, the KD trials show that up to 50% of children on KD treatment can have some or all AED discontinued.⁷ In general these patients have diagnoses of epileptic encephalopathies (eg, Doose syndrome²⁸ and treatment-resistant infantile spasm²⁹).

Side Effects

There are no treatments without side effects and KD is no exception. In the past 100 years, we have come to understand common side effects and how to prevent or treat them. Still lacking are data regarding the true incidence or prevalence of side-effects among centers using KD treatment.

Short-term side effects are all related to metabolic changes associated with carbohydrate restriction and fatty-acid oxidation with production of acidic ketone bodies. Hypoglycemia occurs in approximately 50% of patients when the CKD is introduced quickly. It takes several days for the gluconeogenic processes to be upregulated (Figure 1). A slower advancement of KD ratios and acute treatment with small amounts of carbohydrates (10-20 grams, enough to correct hypoglycemia without abolishing ketosis) is the typical treatment.

The combination of high-acid load and high-fat meals can result in vomiting when the diet is started. Correction of acidosis is important particularly in young children whose kidneys are immature. This is done by adding either citrates (eg, an oral supplement) or with intravenous bicarbonate. When persistent, vomiting can be treated with ondansetron. The most common side effects encountered with KD are gastrointestinal symptoms including constipation and gastroesophageal reflux (GERD). Constipation occurs because

dietary fiber is present only in carbohydrates; it can be treated by adding more oils to the diet (eg, medium-chain triglyceride oil in the food or polyethylene-glycol. For treatment of GERD, H₂-blockers and pump inhibitors are used.³⁰

Hyperlipidemia often develops in the first few months of treatment; up to 50% of patients may have high lipids at some time during KD treatment. This is often due to lack of variety, consuming the same meal repeatedly (eg, a bacon and egg kick), and lack of polyunsaturated fat types. Once KD is established and well-tolerated, more oils can be incorporated, and normal lipid values return. The KD does not appear to cause atherosclerotic changes.³¹ Longer-term side effects include kidney stones in 10% to 15% of patients; kidney stones in patients on KD are typically composed of uric acid rather than calcium. Maintaining good hydration and citrates are both helpful preventive measures for kidney stones. Children who are treated with KD for many years may be shorter than predicted because of height deceleration that is now clearly established as a longer-term side effect in children on KD therapy.³² A growth spurt often occurs after KD is discontinued, this may also be associated with entering puberty more quickly which is also associated with having a shorter adult height. High ketones prevent normal bone mineral content deposition.³³ Hormonal changes and lower amounts of insulin like growth factor 1 (IGF-1) likely contribute to both.³⁴ For young children, meeting adequate protein intake is essential to maximizing growth. Screening with dual-energy x-ray absorptiometry scan, maximizing vitamin D and calcium, and using a stander in non-ambulatory patients are all good preventive measures.³⁰

Management

The use of the KD has spread across the world and this treatment is now utilized for treating patients with epilepsy in over 50 countries on 4 continents. Managing KD is not something taught by reading a few articles or books. Training for new centers is provided by some of the larger centers, and organizations like the Charlie Foundation, or Matthew's Friends, whose mission is spreading the use of KD treatments. Keto University, 2- to 3-day seminars sponsored by Nutricia North America (Danone), is another source of education. There remain variations between centers about specific management details, but larger international groups have come together to publish international guidelines, initially in 2008 and a recent second version 2018.⁷ ■

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