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Ketogenic diet

CAUTION: Don't confuse the Modified Atkins Diet, a form of the ketogenic diet, with the Atkins diet. Also, the ketogenic diet should not be confused with "Keto" dietary supplements that are marketed for inducing ketosis and contain ingredients such as 1,3-Butanediol, Beta-Hydroxybutyrate (BHB), and Medium Chain Triglycerides (MCTs).

Other Common Names

- Classical Ketogenic Diet, Classic Ketogenic Diet, Classic Long-Chain Triglyceride Ketogenic Diet, Keto Diet, LCD, LCHPD, Low-Carb Diet, Low-Carbohydrate Diet, Low-Carbohydrate High-Protein Diet, Low Carb Diet, Low Carbohydrate Diet, Low Glycemic Index Treatment, Medium Chain Triglyceride Diet, Modified Atkin's Diet, Very Low Carbohydrate Diet, Very-Low-Carbohydrate Ketogenic Diet.

Overview

The ketogenic diet requires a high intake of fat and very low intake of carbohydrates, which causes fat to be broken down into ketone bodies for energy. The classic ketogenic diet, which has been used since the 1920s to reduce seizures in children, involves obtaining total energy in a 4:1 ratio of fat to carbohydrate and protein. Other less restrictive forms of the ketogenic diet, such as the modified Atkins diet, the medium chain triglyceride diet, and the low glycemic index diet, have become popular for weight loss (96897,98417,96979).

Safety

LIKELY SAFE ...when used orally and appropriately, short-term. The ketogenic diet has been used with apparent safety in clinical trials for up to 1 year (96907,96951,96952,96955,96956). The severity of reported adverse effects usually depends on the extent of carbohydrate restriction (96954,105929).

There is insufficient reliable information available about the safety of the ketogenic diet when used long-term, in part because long-term adherence rates are low (105929). Limited observational research has found that a lower carbohydrate intake (39% or less of total daily energy) is associated with a higher risk of mortality when compared with higher intakes of carbohydrates. The lowest risk of mortality is associated with a carbohydrate intake of 50% or 55% of total daily energy (105922,105923,105924). However, these findings are not specific to ketogenic diets, which usually involve restricting carbohydrate intake to about 10% of total energy daily. Additionally, carbohydrate

restriction is correlated with higher mortality when the diet consists of high amounts of saturated animal fat and nutrient-poor carbohydrates (105922,105928,105929). As with any diet, the consumption of varied, nutrient-rich foods should be encouraged.

CHILDREN: **POSSIBLY SAFE** ...when used orally and appropriately under medical supervision, short-term. The ketogenic diet has been used safely under medical supervision in children starting at the age of 6 weeks (98417,105882). It is important to ensure that a ketogenic diet used in children contains adequate content of the essential nutrients, including trace elements, since deficiencies and corresponding adverse events may occur (100843). The long-term effects of the ketogenic diet in children are not well known. There is evidence from two observational reports that the ketogenic diet is associated with increased risk of bone fractures, kidney stones, and slowed growth in children when used for more than 2 years (98417,102196).

PREGNANCY: Insufficient reliable information available; avoid using unless under medical advisement. In animal models, ketone bodies can cross the placenta and slow prenatal and postnatal growth (97653).

LACTATION: **POSSIBLY UNSAFE** ...when used orally without medical supervision. While rare, there are several case reports of lactation ketoacidosis thought to be associated with adherence to calorie-restricted and non-calorie-restricted ketogenic diets. The increased metabolic demand of breastfeeding, especially if exclusively breastfeeding, may increase the risk of lactation ketoacidosis in these individuals. In addition to metabolic changes, symptoms included nausea, vomiting, dizziness, dyspnea, lethargy, epigastric pain, and chest pain (108227,108235,108236,113888). In one case, the lactation ketoacidosis was life-threatening and required treatment in the intensive care unit with non-invasive ventilatory support and dextrose and insulin infusions (113888). In this case, the patient was following a calorie-restricted, ketogenic diet and had lost 19 pounds over 3 weeks.

Adverse Effects

General: The ketogenic diet is generally well tolerated when followed for up to one year. Ketogenic diets have poor long-term tolerability and are usually not sustainable long-term.

Most Common Adverse Effects:

Dizziness, fatigue, headache, gastrointestinal discomfort, nausea, and weakness; these symptoms are sometimes referred to as the "keto flu". Other common adverse effects include abnormal lipid levels, constipation, dyspepsia, flatulence, osteopenia, vomiting.

Serious Adverse Effects (Rare):

Acute pancreatitis, arrhythmia, deep vein thrombosis, hepatic dysfunction, hypoglycemia, malnutrition, metabolic acidosis, prurigo pigmentosa, thrombocytopenia purpura, and Wernicke's encephalopathy.

- Cardiovascular

Orally, the ketogenic diet has been reported to increase levels of total cholesterol and triglycerides. The development of increased lipid levels can occur in as many as 60% of diet adherents. Plasma lipid levels usually normalize by 12 months, although hypercholesterolemia and hypertriglyceridemia have occurred in some patients (96903,96957,96966,96968,97639,97647,97650,98415,98417,108219)(108222,108232,113885,113890). In very few cases, the ketogenic diet might need to be stopped. Incorporating monounsaturated and polyunsaturated fats into the diet, especially omega-3 fatty acids, decreases the risk of elevated levels of cholesterol and triglycerides in patients following the ketogenic diet (96966).

Less commonly, deep vein thrombosis (96957), cardiomyopathy, and prolonged QT interval potentiating torsade de pointes (98417,105661), ST depressions and T-wave inversions with exertion (113890) have been reported. However, the exact relationship of these adverse effects with the ketogenic diet is unclear. Atherosclerosis and vascular stiffness have been reported rarely, and are possibly related to the high fat intake of most ketogenic diets (98416,98417,96968,113890).

- ## Dermatologic

Orally, the ketogenic diet has been associated with reports of acne and balding, but these are rare (96903,97644). There are more than 20 reported cases of prurigo pigmentosa, commonly referred to as "keto rash", associated with following a ketogenic diet. Most individuals affected were females ages 16-29 years. The duration of diet prior to symptom onset has ranged from 4 to 160 days. Treatment includes an increased carbohydrate intake of at least 50 grams daily, often in combination with a tetracycline-based antibiotic, especially doxycycline (96962,102188,105657,108216,108223,108225,108229,110198,113884).

- ## Endocrine

The ketogenic diet increases the risk of hypoglycemia and metabolic acidosis (98415,98416,96903,105658,113883). Hypoglycemia has been reported in children starting the ketogenic diet in a hospital setting. This is a normal response in many children and levels are monitored until they return to baseline (97651).

- ## Gastrointestinal

The most common adverse effect of the ketogenic diet is constipation, possibly requiring medication (98415,98417,96903,96957,96978,97639,97650,97651,108232,110207)(113876,113877,113878,113880). Severe fecal impaction with a large stool bezoar that required a right hemicolectomy has been reported in a 6-week-old infant on ketogenic formula for refractory epilepsy (113879). Other common mild adverse effects include vomiting, nausea, diarrhea, hunger, reflux, gas, and abdominal discomfort. These can occur in up to 50% of children when the diet is started and may require medications to reduce the symptoms (98416,98417,96903,96954,96970,96978,97639,97650,97651,108217)(108225,110206,113876,113878,113880,113881). Most gastrointestinal adverse effects can be minimized with slight changes in the ratio of fat to protein plus carbohydrate or by initiating the diet at a slower pace (98416,98417). The medium-chain triglyceride diet providing 60% of calories as medium-chain fatty acids is

associated with the greatest gastrointestinal adverse effects. These can be reduced if long-chain fatty acids are substituted for up to half of the medium chain fatty acids (98417).

Rarely, pancreatitis has been reported (98417,108217,108233). In a 9-year-old child with seizure disorder, acute pancreatitis related to implementing a ketogenic diet with medium chain triglycerides has resulted in death (108237). There are also cases of acute pancreatitis in adults following a ketogenic diet (108217,108233). Ketogenic diet-induced hypertriglyceridemia is thought to induce acute pancreatitis in some patients (108233). However, in at least one case, there was no known risk factor or trigger. Since this particular individual followed the ketogenic diet in a cyclical manner (e.g., five days on and two days off), it was hypothesized that these dietary fluctuations may have played a role (108217).

Gallbladder symptoms, including gallstones, have been reported in a few adults and children (96903,97638,97645). Bad breath has been reported rarely (96903,96907). Protein-losing enteropathy has been reported in two children on the ketogenic diet for epilepsy (96971,97646). In one case, the condition was associated with diarrhea and general edema (96971). The children improved after stopping the diet (96971,97646).

- ## Genitourinary

The ketogenic diet was associated with menstrual irregularities in 3% of female patients in one meta-analysis of observational research (96903).

- ## Hematologic

Hyperuricemia is a common mild and transient adverse effect related to a very low-calorie ketogenic diet in obese adults. It has also been reported with high-fat ketogenic diets in children with epilepsy and a few patients with cancer (96957,96970,96978,97650).

In a case report, hyponatremia thought to be related to the ketogenic diet occurred in an adult given the diet for super-refractory status epilepticus (98415). Hypoproteinemia has been reported rarely in case reports of individuals with cancer using the ketogenic diet (96957,96978). Leukopenia, lymphopenia, and thrombocytopenic purpura, thought to be related to the ketogenic diet, have been reported in a few cases of patients with cancer (96957,96970). In one case report, a 2-year-old female following the ketogenic diet for a seizure disorder presented with anemia and neutropenia caused by copper deficiency. The copper deficiency likely occurred due to switching from a ketogenic diet formula to a pureed food-based ketogenic diet that did not provide adequate copper. The anemia and neutropenia resolved after copper supplementation (100843). Thrombocytopenia purpura has also been reported in a few children with epilepsy (97650). Increased risk of bruising has been reported rarely (98416). The exact relationship with the ketogenic diet is unclear, and it is not known if certain diseases or medications make people more susceptible.

- ## Hepatic

Hepatic dysfunction has been reported rarely in children using the ketogenic diet. In some cases, liver problems may be related to reduced levels of carnitine. Use of valproate, other

antiseizure medications, or antituberculosis medications might also increase the risk of hepatotoxicity in children using the ketogenic diet (98417,113875).

- **Immunologic**

Increased risk of infection has been reported rarely, possibly related to low protein intake (98416). Anaphylaxis associated with the ketogenic diet has also been reported rarely (96968). In one case, a 6-year-old male developed a new-onset egg allergy with an anaphylactic reaction following a previous consumption of 10-15 eggs daily for 6 months as part of the ketogenic diet for epilepsy. The new allergy onset was probably attributable to the large intake of eggs (97642).

- **Musculoskeletal**

The ketogenic diet decreases bone mineral density (BMD) and increases the risk of bone fractures when used in children, especially those on antiseizure medication. Supplementation with calcium and vitamin D helps to mitigate these risks but does not eliminate them. The ketogenic diet seems to increase bone calcium loss. Limited research has found benefit in using intravenous bisphosphonates in children for whom supplementation is not enough to improve BMD (98417,96965,102190). In adults, osteopenia, impaired bone remodeling, muscle weakness, and leg cramps have been reported, likely related to dietary insufficiencies from the ketogenic diet (96903,96907,105651). However, there were no adverse effects on bone health in three adults with glucose transporter 1 deficiency syndrome (GLUT-1 DS) following the ketogenic diet for 5 years (97644).

Hypercalcemia, hypercalciuria, and low levels of alkaline phosphatase, parathyroid hormone (PTH), and 1,25-dihydroxyvitamin D associated with the use of the ketogenic diet were reported in at least 4 young children. All children responded well to treatment with calcitonin (96965,113866). In one case, the ketogenic diet was discontinued but hypercalcemia persisted for another 2 months (113866).

Muscle cramps have been reported in clinical research by some individuals following a very low-calorie ketogenic diet (113877).

- **Neurologic/CNS**

Mild headaches, lethargy, and fatigue have been reported rarely, probably related to the reduction in carbohydrate intake. These symptoms are a part of a syndrome called the "keto flu" which sometimes occurs when initiating the ketogenic diet (96903,96954,96970,96978,97650,97651,108225,113877,113878). In a few cases, seizures have worsened. However, this is no more than expected with any treatment for epilepsy (96903).

Some early evidence suggests a slight delay in some cognitive test results with a very low-calorie ketogenic diet for weight loss. However, the clinical significance of this is unclear (97649).

In a case report, a 16-year-old male using the ketogenic diet for about 5 months for extreme

weight loss developed Wernicke's encephalopathy due to thiamine deficiency. Symptoms included double vision and falling. The patient required intravenous thiamine and diet education (108224).

- ### Psychiatric

  Psychosis or hallucinations have been reported in <0.3% of adults on the ketogenic diet (96903).

- ### Renal

  Renal calculi have been reported to occur in as many as 7% of children and 7.9% of adults on the ketogenic diet, due to increased calcium in the blood and urine. The stones contain uric acid, calcium oxalate, and/or calcium phosphate (98416,98417,96903,96965,97650,108220). Discontinuation of the diet or lithotripsy are rarely needed. Oral citrates and adequate hydration are used to prevent stone formation (98416,98417). The ketogenic diet might increase the risk of dehydration and urinary frequency and electrolyte abnormalities such as hyponatremia (98416,96907,96970,98415,108225). Acute kidney injury has been reported in a 36-year-old female with no history of renal disease after following a ketogenic diet for 2 months that had resulted in a 30-pound weight loss (113889).

- ### Other

  Unintentional weight loss is a possible adverse effect of the ketogenic diet (98415,96903,96957,113877). However, weight gain has also been reported (96903). Observational research suggests that use of the ketogenic diet in children aged 0-3 years for at least 1 year for medication-refractory epilepsy is associated with a decrease in height z-scores, suggesting compromised linear growth. This finding was correlated with lower dietary energy intakes when compared to baseline and reference ranges (113887).

Effectiveness

POSSIBLY EFFECTIVE

Diabetes. Following the ketogenic diet seems to improve glycemic control in patients with type 2 diabetes.

Details: Meta-analyses of up to 10 small clinical studies in patients with diabetes, most of whom were taking antidiabetes medications, as well as those with pre-diabetes, shows that following a low or very-low carbohydrate ketogenic diet seems to reduce glycated hemoglobin (HbA1C) by up to 0.6% when compared with following a normal diet or a control diet consisting of any diet commonly recommended to patients with type 2 diabetes, such as a low-calorie diet (105650,108232,110194). A sub-analysis shows that the beneficial effect of the ketogenic diet on HbA1C, when compared to other diets, was limited to the first 6 months (108232). However, another meta-analysis shows that if a very-low carbohydrate ketogenic diet reduces HbA1C at 12 months,

any change is small, and it is unclear if there is any benefit when compared to other dietary strategies (110205).

Some, but not all, research shows that the ketogenic diet reduces levels of fasting blood glucose (105650,108231,108238,110194). Research also suggests that the ketogenic diet can reduce the need for hypoglycemic agents in patients with diabetes (105650,108232). To reduce the risk of hypoglycemia, some studies excluded patients taking insulin and sulfonylureas, while others reduced insulin and sulfonylurea doses before initiation of the ketogenic diet (96954,96955,96956).

Meta-analyses also show that following a low or very-low carbohydrate ketogenic diet for 3 months, and possibly up to 12 months, seems to modestly reduce triglyceride levels in patients with type 2 diabetes when compared with control diets (108230,108232,108238,110194,110205). However, effects on high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol are unclear, with meta-analyses and individual clinical trials identifying increases, decreases, or no change in these levels (108230,108231,108232,108238,110194,110205).

Finally, following a low- or very low-carbohydrate ketogenic diet seems to reduce weight by an average of 2.8 kg over 6 months (108232) or up to about 8.7 kg overall when compared with a control diet (96954,96955,96956,105650,108231,108238).

Epilepsy. Following the classic ketogenic diet seems to be beneficial for various types of drug-resistant epilepsy disorders. Less restrictive ketogenic diets, such as the modified Atkins diet, may be similarly effective.

Details: Numerous low-quality clinical and observational studies suggest that following the ketogenic diet for at least 2 weeks reduces seizures in some patients with medication-refractory epilepsy. Most research has been conducted in children (96897,97636,98416,98417,96903,96904,97637,97639,102109,102110)(102195,108219,110196,110207,113876,113880,113881). A meta-analysis of 8 clinical trials involving 453 pediatric patients with drug-resistant epilepsy shows that following a ketogenic diet for up to 3 months results in a 5.6-fold greater likelihood of a 50% or greater seizure frequency reduction when compared with following a usual diet (108226). An earlier meta-analysis of 4 clinical trials involving 385 similar patients shows similar findings. In addition, this analysis shows that there was a 3-fold greater likelihood of achieving seizure freedom when compared with following a usual diet (105882). An open-label, clinical trial in infants aged 1-24 months with medication-refractory epilepsy shows that following the classic ketogenic diet for 8 weeks is similarly effective as adding another antiseizure medication for reducing the number of seizures, achieving seizure-freedom, and achieving a 50% or greater reduction in seizures (113881). Also, some preliminary clinical research shows that, when added to on-going anti-seizure medication, the modified Atkins diet for 12 weeks is more effective than levetiracetam for increasing the proportion of children with at least a 50% reduction in seizure frequency (110207).

Some clinical research in children shows that following the more restrictive classic ketogenic diet achieves greater seizure reduction when compared with less restrictive ketogenic diets such as the modified Atkins diet (105660,105882,110197), while other clinical trials show the classic ketogenic diet and the modified Atkins diet are similarly effective for achieving seizure freedom over 3 months of observation (113880) and over 6 months of observation (113876). Additionally, the classic ketogenic diet and the modified Atkins diet are similarly effective for achieving seizure frequency reductions of at least 90% (105660,105882,110197,113880), achieving seizure frequency reductions of at least 50% (113876,113880), and reducing the severity of seizures (113876). Approximately 43% of patients were able to discontinue between 1 and 2 antiepileptic medications from their treatment regime after 6 months on both the classic ketogenic diet and the modified Atkins diet (113876). Another individual

study in adolescents and young adults shows that increasing the fat content of a ketogenic diet from a ratio of 2 grams of fat per 1 gram of protein plus carbohydrates (2:1 ratio) up to a ratio of 3:1 is no more effective for seizure reduction than the 2:1 ratio diet. The 3:1 ratio diet was also associated with lower adherence (108219).

Evidence in adults is very limited. A meta-analysis of 2 small clinical trials in adults with drug-resistant epilepsy did not find a significant benefit of following the ketogenic diet when compared with control. However, there was a non-significant trend towards a greater likelihood of achieving a 50% or greater seizure frequency reduction when compared with control (105882).

The 2018 guidelines from the International Ketogenic Diet Study Group recommend that the ketogenic diet is followed for at least 3 months to determine its efficacy. Also, while there is no maximum duration limit for the ketogenic diet under medical supervision, it is typically stopped after 2 years in patients with a clinical response. For certain types of seizures, such as infantile spasms, the diet may be discontinued after even shorter periods (98417). Specific conditions for which the ketogenic diet has been shown to reduce medication-refractory seizures include glucose transporter 1 deficiency syndrome, pyruvate dehydrogenase deficiency and other mitochondrial diseases, epilepsy with myoclonic-atonic seizures, West syndrome or infantile spasms, tuberous sclerosis complex, and Dravet syndrome (98417,105663,105666,110206,113876,113880). The ketogenic diet has also been assessed for many other types of refractory seizures, including seizures of unknown etiology, but the evidence of benefit is limited (98417,113876).

Obesity. The ketogenic diet seems to help reduce weight in overweight and obese adults, although it is unclear whether it is superior to other diets. Oftentimes the ketogenic diet is combined with calorie restriction and/or exercise.

Details: Several low-quality studies in overweight and obese adults show that following a ketogenic diet that limits carbohydrate intake to no more than 20 grams daily, and does not limit calories, for 6-12 months reduces body weight by about 10% to 30% when compared to baseline (96907,96951,96952,96956). Other research has also yielded promising results. One meta-analysis pooled the results from 7 small studies that utilized either a very low- or low-carbohydrate diet, with or without calorie restriction, in obese and overweight adults. This analysis shows that following one of these diets for 1-12 months seems to reduce weight by an average of 7.8 kg in patients with diabetes and an average of 3.8 kg in patients without diabetes when compared with various control diets. It is unclear how the variability in carbohydrate restriction or calorie restriction may have affected the outcomes (105650). Another meta-analysis of 3 studies in overweight adults and 2 studies in obese adults shows that following the ketogenic diet without calorie restriction but along with a regular exercise regimen reduces weight by an average of 4-6 kg when compared with a control diet, with or without exercise (105647). It is unclear how much of the weight loss benefit is due to the ketogenic diet, exercise, or the combination.

The ketogenic diet has been compared with other diets for weight loss in overweight or obese individuals. Some research suggests that the ketogenic diet may reduce weight slightly more than a low-fat diet (96905,110204). A meta-analysis of 13 clinical studies in 1577 obese adults shows that following a ketogenic diet that limits carbohydrate intake to less than 50 grams daily for 12-24 months reduces body weight by an average of 0.9 kg more than a low-fat diet (<30% of energy from fat) (96905). Clinical research shows that following a low-carbohydrate ketogenic diet for 6 months reduces body weight, body mass index (BMI), fat mass, and visceral fat, by an additional 8.3 kg, 3.2 kg/m^2, 2.6%, and 1.3 liters, respectively, when compared to a low-calorie and low-fat diet. However, muscle mass loss was also increased by approximately 1.5 kg (110204). The National Lipid Association (NLA) Nutrition and Lifestyle Task Force concludes that low- and very low-carbohydrate diets are no

better than other diets for weight loss and considers carbohydrate-restricted diets a reasonable option when followed for up to 2-6 months. Because long-term carbohydrate restriction may pose adherence difficulties, the NLA recommends a diet with moderate carbohydrate intake for durations longer than 6 months (105896). However, this recommendation is not specific to the ketogenic diet and is based on studies evaluating various non-ketogenic low-carbohydrate diets such as the Atkins and South Beach diets. A large clinical study in adults with overweight or obesity shows that following a very low-calorie ketogenic diet takes one month to achieve a 5% weight loss, compared with 3 months in adults following a Mediterranean diet providing an energy deficit of approximately 500 kcals daily. However, there were no differences between groups in absolute weight loss or changes in BMI, and changes in waist circumference, fat mass, and fat-free mass were modestly more beneficial in females and individuals under the age of 50 years consuming the hypocaloric Mediterranean diet when compared to the very low-calorie ketogenic diet (109889).

The effect of the ketogenic diet on weight loss in patients with type 2 diabetes or polycystic ovary syndrome (PCOS) has also been investigated (96955,108218,108231,110194,110202). Individual clinical trials and a meta-analysis of clinical research in overweight or obese patients with type 2 diabetes show that following a ketogenic diet with a carbohydrate intake of up to 50 grams daily increases weight loss (96955,108231,110194). A meta-analysis of clinical research also shows that following a ketogenic diet resulted in a reduced weight circumference, without affecting BMI (110194). One of these studies, shows that following the ketogenic diet with no calorie restriction for 8 months increases weight loss to about 10 kg (5% to 10%) when compared with a control diet (96955). In another, the ketogenic diet was used in conjunction with caloric restriction, providing 1500 kcals daily for 12 weeks in patients (108218). In patients with PCOS, a very-low-calorie ketogenic diet, providing 600 to 800 kcals daily, was used for 45 days or 4 weeks with a re-introduction diet over an additional 8 weeks, resulting in weight loss when compared with baseline (108218,110202). In these latter studies, it is unclear how the calorie restriction may have affected the outcomes.

The ketogenic diet is also of interest for its potential effects on cholesterol and triglyceride levels. One meta-analysis in patients with obesity shows that various forms of a low-carbohydrate ketogenic diet, usually in combination with very low caloric intake, is no more beneficial than balanced low-calorie or low-fat diets for reducing levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, or triglycerides, or for increasing levels of high-density lipoprotein (HDL) cholesterol (108221). However, some clinical research shows that following a low-carbohydrate ketogenic diet for 6 months is modestly more beneficial than a low-calorie and low-fat diet for reducing triglyceride levels (110204).

There is limited evidence on the use of the ketogenic diet for weight loss in children and adolescents. One preliminary clinical study in obese children and adolescents shows that following a ketogenic diet initially providing less than 20 grams of carbohydrates daily, and increasing to 30-40 grams daily for 6 months, reduces weight by approximately 8 kg and fat mass by 7 kg when compared with baseline. However, this weight loss is similar to that observed in patients following a typical low-calorie diet (96906).

INSUFFICIENT RELIABLE EVIDENCE to RATE

Alcohol use disorder. It is unclear if following the ketogenic diet is beneficial in patients with alcohol use disorder.

Details: A small clinical study in patients hospitalized for alcohol use disorder shows that following the ketogenic diet for 3 weeks seems to reduce benzodiazepine use and tends to reduce cravings when compared with a standard diet (105664).

Alzheimer disease. It is unclear if following the ketogenic diet is beneficial in patients with Alzheimer disease.

Details: One small clinical study in patients with probable Alzheimer disease suggests that following a ketogenic diet consisting of 58% fat, 29% protein, 7% fiber, and 6% carbohydrate for 12 weeks seems to improve activities of daily living and quality of life when compared with following a usual diet. Cognition was not significantly different between groups at the end of the study, although there was a non-significant trend towards an attenuated decline in cognitive scores when compared with the control group (105883).

Athletic performance. Following the ketogenic diet is unlikely to benefit athletic performance. It is unclear if following the ketogenic diet worsens athletic performance.

Details: Meta-analyses of clinical research in trained adults shows that following a low-carbohydrate high-fat ketogenic diet for 3-12 weeks while undergoing concurrent training does not affect lean mass, body fat, body mass, maximal oxygen consumption, or athletic performance, when compared with concurrent training with other dietary strategies (110199,110201). One study included in one analysis shows that following the ketogenic diet for 30 days did not affect strength or power in soccer players when compared with a Western diet providing isocaloric amounts of protein at 1.8 grams/kg daily. In this study, the group consuming the ketogenic diet had a greater reduction in fat mass (108215). Another small study in trained females shows that following a ketogenic diet for 8 weeks results in smaller increases in strength while squatting and bench pressing when compared with following a non-ketogenic diet (105662).

Other small individual trials have been conducted. One very small clinical study in experienced male cyclists shows that following a ketogenic diet consisting of 15% of energy from carbohydrates for 4 weeks decreases maximal workload, but seems to modestly increase maximal oxygen uptake during a high-intensity cycling test when compared with consuming a standard Western diet (96958). One small clinical study in exercise-trained, healthy adults shows that following a low-carbohydrate ketogenic diet for 4 days reduces peak power and total distance covered while running when compared with following a high carbohydrate diet (102113). Additionally, a small trial in untrained, healthy adults shows that following a ketogenic diet for 3 days reduces exercise efficiency during high-intensity, but not low- or moderate-intensity, graded treadmill exercise when compared with a mixed diet. Ratings of perceived exercise during low and high intensity exercise were also higher after the ketogenic diet when compared with the mixed diet (113882). These studies are limited by short duration of the diet and small sample sizes.

Autism spectrum disorder. It is unclear if following the ketogenic diet is beneficial in patients with autism spectrum disorder.

Details: A small single-center clinical study in children aged 3-9 years with autism spectrum disorder shows that following the modified Atkins diet (MAD) for 6 months seems to improve scores on the Childhood Autism Rating Scale (CARS) and the Autism Treatment Evaluation Checklist (ATEC) when compared with following a nutritionally balanced control diet. Following the MAD seems to be no better than following a gluten- and casein-free diet (98723). These findings are limited by the small study size and the 33% dropout rate in the MAD group due to poor diet adherence.

Bipolar disorder. Although there is interest in the ketogenic diet for bipolar disorder, there is insufficient reliable information about the clinical effects of the ketogenic diet for this condition.

Breast cancer. It is unclear if following the ketogenic diet is beneficial in patients with breast cancer.

Details: Small clinical studies in patients with breast cancer show that following a ketogenic diet does not improve quality of life when compared with a standard diet (105652,110208). One small clinical study in patients with advanced or metastatic breast cancer shows that following a ketogenic diet with 6% of calories from carbohydrates, 19% from protein, and 75% from fat for 12 weeks also does not improve physical activity when compared with an equicaloric control diet (105652).

Cancer. It is unclear if following the ketogenic diet is beneficial in patients with cancer.

Details: Meta-analyses of mainly small clinical trials in patients with various types of cancer show that following a ketogenic diet for 1-20 weeks modestly reduces body weight and fat mass when compared with a control diet, usually a standard diet. Most research also shows that there was no effect on markers of liver or kidney health. However, the evidence is mixed with respect to some glycemic and lipid indices, or quality of life (110203,110208).

Cerebral palsy. Although there is interest in the ketogenic diet for cerebral palsy, there is insufficient reliable information about the clinical effects of the ketogenic diet for this condition.

Cognitive impairment. It is unclear if following the ketogenic diet is beneficial in patients with cognitive impairment.

Details: A small clinical study in older patients with mild cognitive impairment shows that following a modified Mediterranean ketogenic diet (MMKD) for 6 weeks improves memory, but not story recall or general cognition, when compared to baseline (102194). This study is limited by small size, short duration, lack of comparison to control group, and a potential Hawthorne effect.

HIV/AIDS-related dementia. It is unclear if following the ketogenic diet is beneficial in patients with dementia related to HIV/AIDS.

Details: A small clinical study in adults over 50 years old with HIV-associated cognitive impairment shows that following the ketogenic diet for 12 weeks improves executive function and processing speed when compared with following a regular diet. The benefit was no longer present 6 weeks after discontinuing the ketogenic diet (102193).

Hypertension. It is unclear if following the ketogenic diet is beneficial in patients with hypertension.

Details: Preliminary clinical research in overweight or obese individuals with or without hypertension shows that following a ketogenic diet for 48 weeks reduces systolic and diastolic blood pressure by 6 mmHg and 5 mmHg, respectively, when compared to baseline. When compared with patients taking orlistat therapy combined with a low-fat diet, these improvements are statistically significant (96907). Since this study included obese patients with or without hypertension, the effects of the ketogenic diet in only patients with hypertension is unclear.

McArdle disease. It is unclear if following the ketogenic diet is beneficial in patients with McArdle disease.

Details: A small clinical study in adults with McArdle disease shows that following a modified ketogenic diet providing 75% to 80% of dietary energy as fat, 15% as protein, and 5% to 10% as carbohydrate for 3 weeks increases maximal exercise capacity by 20%, but does not improve heart rate responses during submaximal cycle exercise, when compared with an isocaloric, balanced control

diet. Self-reported McArdle disease symptoms and scores on the Short-form Health Survey (SF-36) also improved with the ketogenic diet when compared with the control diet. Approximately 67% of the dietary energy in both diets was provided by specific liquid supplements; Ketocal (Nutricia) in the ketogenic diet group and Fortini (Nutricia) in the control group (113878).

Migraine headache. It is unclear if following the ketogenic diet is beneficial in patients with migraine.

Details: A small clinical study in patients with high-frequency episodic migraine (8-14 days per month) shows that following a very low-calorie ketogenic diet for 8 weeks reduces monthly migraine days by approximately 4 days when compared with a hypocaloric balanced diet (HBD). Additionally, 24 weeks later, after both groups had been following the HBD for at least 11 weeks, monthly migraine days were still lower, by about 3 days, in those who had previously followed the ketogenic diet (113877). Another preliminary clinical study shows that eating a low-fat and very low-calorie ketogenic diet providing approximately 15 grams of fat, 30 grams of carbohydrate, and 800 kcal or less daily reduces the number of migraine attacks per month by about 2 and the number of days with a headache by about 4 when compared to baseline. This improvement is significantly better than a standard low-calorie diet of 1200-1500 kcal, which resulted in no improvements over this time period (97641). Also, observational research suggests that following a ketogenic diet for 3 months is associated with 6 fewer headache days and 6 fewer days requiring acute medication. Although body weight and fat mass were modestly reduced, there was no correlation between weight loss and headache response (110200).

Multiple sclerosis (MS). Although there is interest in the ketogenic diet for MS, there is insufficient reliable information about the clinical effects of the ketogenic diet for this condition.

Muscle fatigue. It is unclear if following the ketogenic diet helps to prevent muscle fatigue.

Details: A small clinical study in young healthy females shows that following a ketogenic diet high in saturated fatty acids for 4 weeks seems to speed up the onset of muscle fatigue during exercise and seems to increase fatigue during regular life activities when compared with following a normal diet (105659).

Narcolepsy. Although there is interest in the ketogenic diet for narcolepsy, there is insufficient reliable information about the clinical effects of the ketogenic diet for this condition.

Nonalcoholic fatty liver disease (NAFLD). It is unclear if following the ketogenic diet is beneficial in patients with NAFLD.

Details: One very small clinical study in patients with NAFLD shows that following a ketogenic diet comprised of 4% carbohydrates, 72% fat, and 24% protein for 14 days seems to reduce hepatic steatosis when compared with baseline (105926). Another very small clinical study in patients with NAFLD shows that following a ketogenic diet restricted to <20 grams carbohydrates daily for 2 weeks reduces hepatic triglycerides to a slightly greater degree when compared with following a calorie restricted diet of 1200-1500 kcal daily (105927). These findings are limited by small study size and short duration.

Pain (chronic). It is unclear if following the ketogenic diet is beneficial for reducing chronic pain.

Details: A small clinical trial in patients with chronic pain due to conditions such as spinal pain and fibromyalgia shows that following a whole food-based ketogenic diet for 12 weeks modestly

reduces pain when compared with baseline. However, it was no more effective than consuming a minimally processed whole food diet (108228).

Parkinson disease. It is unclear if following the ketogenic diet is beneficial in patients with Parkinson disease.

Details: A small clinical study in patients with Parkinson disease shows that following the ketogenic diet for 8 weeks does not improve motor function, but does modestly improve non-motor measures such as mood, cognition, urinary problems, and pain, when compared with following a low-fat, high-carbohydrate diet (102111). Another small clinical study in patients with a voice disorder secondary to Parkinson disease shows that following a ketogenic diet for 3 months seems to improve Voice Handicap Index-10 scores when compared with baseline, but not when compared with following a regular diet (105653). This study may have not been adequately powered to detect a difference between groups.

Polycystic ovary syndrome (PCOS). It is unclear if following the ketogenic diet is beneficial in patients with PCOS.

Details: A small clinical study in obese patients with PCOS shows that following the ketogenic diet for 12 weeks reduces levels of liver enzymes, shortens the menstrual cycle, and reduces weight when compared with a control diet (105656). Another small study in obese patients with PCOS shows that following a very low calorie ketogenic diet providing 600 to 800 kcals daily for 4 weeks, followed by 4 weeks each of a low calorie diet providing 1200 to 1500 kcals daily and a maintenance balanced diet providing 1500 to 2000 kcals daily, modestly reduces weight, body mass index, and waist circumference, and improves markers of ovarian reserve quality and luteal function, when compared with baseline (110202).

Psoriasis. Although there is interest in the ketogenic diet for psoriasis, there is insufficient reliable information about the clinical effects of the ketogenic diet for this condition.

Schizophrenia. Although there is interest in the ketogenic diet for schizophrenia, there is insufficient reliable information about the clinical effects of the ketogenic diet for this condition.

Seizures. Although most evidence suggests that the ketogenic diet is beneficial for refractory epilepsy in children, it is unclear if it is beneficial in patients with non-epileptic seizures.

Details: Preliminary clinical research in adults without a history of epilepsy that are experiencing super-refractory status epilepticus shows that providing a ketogenic diet via gastrostomy tube was associated with seizure resolution within a median of 5 days in 79% of those that were able to complete treatment (98415).

Stroke. Although there is interest in the ketogenic diet for stroke, there is insufficient reliable information about the clinical effects of the ketogenic diet for this condition.

More evidence is needed to rate the ketogenic diet for these uses.

Administration / Application

- The ketogenic diet was originally designed to be high in fat and very low in carbohydrates. This type of ketogenic diet is used in the treatment of epilepsy. However, variations of the ketogenic diet, with low or very low levels of calories and fat, are used for other purposes. Carbohydrate-containing foods that are typically excluded or consumed in very low levels in the ketogenic diet include fruits, vegetables, grains and enriched grains, calcium-containing foods such as milk, and non-animal sources of protein. Thus, the ketogenic diet requires supplementation with non-carbohydrate containing sources of these nutrients, including a multivitamin and mineral for B vitamins and selenium, as well as additional vitamin D and calcium at age-appropriate recommended levels (98417). Although some experts suggest regular supplementation with carnitine, other experts believe that carnitine supplementation is needed only if levels are low or if symptoms of hypocarnitinemia exist (98417).

  Classic ketogenic diet: The classic ketogenic diet uses long-chain fatty acids in dietary triglycerides as the main source of fat (98417,96979). The most common ratio of macronutrients in the classic ketogenic diet is fat 4 grams to protein plus carbohydrate 1 gram (4:1 ratio). This results in 90% of calories from fat (96897,98417,96969,96979). In children, the classic ketogenic diet can be initiated at a ratio of 4:1 and then possibly reduced to 3:1. In infants, the diet with a ratio of 3:1 is often used (98417). The classic ketogenic diet is most commonly used by individuals with seizures and is usually started in the hospital (98417). The diet can be consumed as food or as a liquid, formula-based diet. The liquid diet is used by infants or children that need enteral feeding; food can be pureed if needed (98417). Oral citrates are sometimes recommended to children following the ketogenic diet to prevent kidney stones (98417). Over-the-counter and prescription drugs and vitamin and mineral supplements containing carbohydrates must be avoided by those following the classic ketogenic diet for epilepsy to adhere to the low carbohydrate nature of the diet (98417). Seizures can return with the inclusion of very small amounts of carbohydrate from these sources.

  Medium chain triglyceride diet: The medium-chain triglyceride diet is similar to the classic ketogenic diet. However, it uses medium-chain fatty acids as the main source of fat and energy. Medium-chain triglycerides are less common in foods but yield more ketones in the same amount of energy, allowing for more food choices containing carbohydrates and protein. The ratio of fat to protein plus carbohydrate can be as low as 1:1 (98417,96979). In some cases, medium-chain oils are added to the classic ketogenic diet (98417). Do not confuse ketogenic diets such as the medium chain triglyceride diet with "keto diet supplements", which are marketed for inducing ketosis despite a lack of supportive evidence. These supplements usually contain ingredients such as 1,3-butanediol, **Beta-Hydroxybutyrate (BHB)**, and **Medium Chain Triglycerides (MCTs)**.

  Modified Atkins diet: The modified Atkins diet is a more recent version of the classic ketogenic diet. It is easier to use and does not require precise weighing of ingredients. It is more tolerable and is generally preferred by adults (96897,98417,96979). The ratio of fat to protein plus carbohydrate in the modified Atkins diet can be as low as 1:1 or as high as 4:1. Although intakes of carbohydrate are very low (<20-30 grams depending on age), there is no limitation in calories or protein, unlike the Atkins diet. At present, this variation is not generally used by children under the age of 2 years, as these patients often have less difficulty following a classic ketogenic diet (98417,96969,96979).

  Modified Mediterranean diet: The modified Mediterranean diet is a variation of the classic ketogenic diet. It is a very low carbohydrate diet modeled on a Mediterranean diet. It focuses on protein sources that are low in saturated fat such as fish and lean meats, increased olive

oil, fruit, vegetable and whole grain consumption, and a daily glass of wine (102194).

Low glycemic index treatment: The low glycemic index treatment is another more recent version of the classic ketogenic diet. It is easier to use and does not require precise weighing of ingredients. It is more tolerable and is generally preferred by adults (96897,98417,96979). The low glycemic index treatment allows for carbohydrate intake levels of 40-60 grams daily, instead of the more common 10-20 grams. However, the carbohydrates consumed have glycemic indices of <50. This variation is not well studied for epilepsy (98417,96969,96979). The low glycemic index treatment is more commonly started as an outpatient (98417).

Interactions with Drugs

ANTICOAGULANT/ANTIPLATELET DRUGS

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Moderate • Occurrence = Unlikely • Level of Evidence = **B**

Although there is some concern that the ketogenic diet might have additive effects when used with anticoagulant and antiplatelet drugs, most clinical research does not show this effect.

Details

One small observational study found that the ketogenic diet was associated with prolonged bleeding times in 16 of 51 (31%) children with epilepsy who were also on chronic anticonvulsant therapy (97652). However, a larger observational study of 162 children with epilepsy taking chronic anticonvulsants has found that following the ketogenic diet does not increase the risk of bleeding, even in the 25 children undergoing surgery. Research in adults also has not reported changes in bleeding time (105655).

ANTICONVULSANTS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Following the ketogenic diet may reduce the levels of certain anticonvulsants, although the clinical significance of this effect is unclear.

Details

Pharmacokinetic research in patients chronically taking up to 4 antiepileptic drugs shows that following a modified Atkins diet for 4-12 weeks reduces the average anticonvulsant serum concentrations by 10.5% to 13.5% (range 7% to 19%) without affecting overall seizure control. Antiepileptic agents taken by these patients included carbamazepine, oxcarbazepine, topiramate, valproate, clobazam, nitrazepam, lamotrigine, zonisamide, and others. Levels of oxcarbazepine and levetiracetam did not seem to be significantly affected after the initiation of the ketogenic diet (97656,105665). Additionally, a small clinical study in children with drug-refractory epilepsy taking a variety of anticonvulsant medications shows that following a ketogenic diet for 12 weeks reduces serum concentrations of clobazam and its active metabolite desmethylclobazam, both by 38%, and lamotrigine by 15% without affecting overall seizure control. Levels of levetiracetam, topiramate, and valproic acid were not significantly reduced (113891). Serum levels of anticonvulsants should be monitored in patients following a ketogenic diet.

ANTIDIABETES DRUGS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **B**

Theoretically, following the ketogenic diet while using antidiabetes drugs might increase the risk of hypoglycemia.

Details

The ketogenic diet involves a very low intake of carbohydrates, which can result in decreased blood glucose levels in patients taking antidiabetes drugs. In some patients, the need for antidiabetes drugs is reduced (96907,96954,96955,96956). Hypoglycemia has also occurred in some individuals without diabetes, although this is uncommon (98415,96903).

CARBONIC ANHYDRASE INHIBITORS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = Moderate • Occurrence = Possible • Level of Evidence = **D**

Theoretically, combining carbonic anhydrase inhibitors with the ketogenic diet can increase the risk of kidney stones.

Details

Carbonic anhydrase inhibitors can increase the risk of kidney stones by worsening metabolic acidosis. The ketogenic diet can also increase the risk of metabolic acidosis and kidney stones. The combination of carbonic anhydrase inhibitors and the ketogenic diet seems to worsen metabolic acidosis in some patients. Bicarbonate levels should be measured in individuals on the ketogenic diet using carbonic anhydrase inhibitors (98416,98417).

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS

Interaction Rating = **Moderate** Be cautious with this combination.

Severity = High • Occurrence = Possible • Level of Evidence = **C**

Combining SGLT2 inhibitors with the ketogenic diet can increase the risk of ketoacidosis.

Details

The National Lipid Association Nutrition and Lifestyle Task Force recommends that patients following diets that restrict carbohydrates to 20-50 grams daily, such as the ketogenic diet, avoid taking SGLT2 inhibitors. This combination increases the risk of developing ketoacidosis (105896,108234).

VALPROATE

Interaction Rating = **Minor** Be watchful with this combination.

Severity = Moderate • Occurrence = Unlikely • Level of Evidence = **D**

There is some concern that the ketogenic diet might have additive hepatotoxic effects when used with valproate.

Details

Valproic acid and the ketogenic diet are commonly combined in patients with epilepsy (98417,97650). However, hepatic dysfunction has been reported in children using the ketogenic diet, with evidence from some cases suggesting that the risk is increased in children also taking valproic acid. Tapering the medication and the diet has allowed for successful re-introduction of the diet in persons affected with liver injury (98417). There is also some concern that combining

valproic acid with the ketogenic diet might reduce the effects of both interventions. Valproic acid can inhibit ketosis in children using the ketogenic diet (98417,97650). In at least two cases, valproate levels in the blood were decreased by as much as 32% in adults using the ketogenic diet (97656). However, these risks appear to be rare.

Interactions with Supplements

HERBS AND SUPPLEMENTS WITH HYPOGLYCEMIC POTENTIAL: The ketogenic diet seems to lower blood glucose levels.

Details

Theoretically, the ketogenic diet might have additive effects if used with herbs that decrease blood glucose levels (96907,96954,96955,96956). See products with hypoglycemic potential **here**.

Interactions with Conditions

CARDIOVASCULAR CONDITIONS

Theoretically, the ketogenic diet might worsen some cardiovascular conditions. The ketogenic diet has been associated with reports of vascular stiffness, atherosclerosis, prolonged QT interval, and cardiomyopathy (95726,98416,98417,96957,96968). Patients with atrial fibrillation, heart failure, or other cardiovascular conditions might be at higher risk for cardiovascular complications when following the ketogenic diet (105896).

DIABETES

Following a low-carbohydrate ketogenic diet might increase the risk for diabetic ketoacidosis (DKA) in some patients with diabetes. In one case, a 22-year-old female with undiagnosed type 1 diabetes developed DKA and dyspnea after following a low-carbohydrate ketogenic diet for 4 days (105649). In another case, a 30-year-old male with type 2 diabetes developed DKA after following a low-carbohydrate ketogenic diet for 2 months (106044).

GASTROESOPHAGEAL REFLUX

Theoretically, pre-existing gastroesophageal reflux might be exacerbated when following a ketogenic diet. A high-fat ketogenic diet can delay gastric emptying and increase the risk of reflux (98416).

HYPERLIPIDEMIA

The ketogenic diet might worsen hyperlipidemia. It has been reported to cause abnormal lipid parameters, including increased levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides, in up to 60% of patients in some clinical research. While plasma lipid levels usually normalize by 12 months, hypercholesterolemia and hypertriglyceridemia have occurred in some patients (98415,98417,96903,96957,96966,96968,97639,97647,97650,105648). Lipid levels should be monitored, and the diet altered as needed to increase the dietary intake of medium chain fats, monounsaturated fats, and omega-3 fats (98416,98417).

LIVER DISEASE

The ketogenic diet can increase the risk of liver disease in some people, especially those using valproate or those deficient in carnitine. Use the ketogenic diet with caution in patients with liver disease (98416,98417,105929).

METABOLISM DISORDERS

The ketogenic diet is contraindicated for certain metabolic disorders. The ketogenic diet causes a shift in the primary energy source of foods from carbohydrates to fats. Patients with disorders of fat metabolism, transport, and oxidation could deteriorate with the ketogenic diet, resulting in coma or death. Examples of metabolic disorders for which the ketogenic diet is contraindicated include primary carnitine deficiency, carnitine palmitoyl transferase deficiencies, carnitine translocase deficiency, beta-oxidation defects, acyl dehydrogenase deficiencies, gluconeogenesis defects, some glycogen storage diseases, ketolysis or ketogenesis defects, hyperinsulinism in the absence of insulin-suppressing drugs, pyruvate carboxylase deficiency, and porphyria (98416,98417).

KIDNEY DISEASE

The ketogenic diet can exacerbate kidney disease and increase the risk of kidney stones in patients with or at risk for kidney disease. Use the ketogenic diet with caution in patients with kidney disease (98416,98417,105929).

OSTEOPOROSIS

Following the ketogenic diet long-term can increase the risk of osteoporosis in some people. The ketogenic diet has been associated with decreased bone mineral density (BMD) (105896). Ensure adequate calcium and vitamin D intake and monitor BMD in patients at risk for osteoporosis.

PANCREATITIS

The ketogenic diet can increase the risk of pancreatitis in some people. Use the ketogenic diet cautiously and monitor for symptoms in patients who are at risk for pancreatitis, such as those with a history of hypertriglyceridemia-associated acute pancreatitis or severe hypertriglyceridemia (105896,108233).

PERIOPERATIVE

Patients on the restrictive classic ketogenic diet are limited to very small amounts of carbohydrates daily. During surgery, medications containing carbohydrates or converting to carbohydrates can alter metabolism. These include cardiopulmonary bypass solutions, lactated ringers, mannitol, and Plasma-Lyte. In patients on a stable ketogenic diet for epilepsy, these compounds need to be replaced to avoid exposure to a significant amount of carbohydrates over a short period of time (97652).

Interactions with Lab Tests

ALCOHOL BREATHALYZER

In rare cases, the metabolic byproducts of the ketogenic diet could cause a false positive on alcohol breathalyzer tests using electrochemical oxidation. In one case report, a 59-year-old male that had never consumed alcohol was not able to start a car fitted with an alcohol ignition interlock device after following a very low-calorie ketogenic diet for 3 weeks. It is theorized that the resulting acetone in the body was reduced to isopropanol and falsely detected as ethanol in the breath (96967).

Theory / Mechanism of Action

General: The ketogenic diet is low in carbohydrates. Since the primary source of fuel for the brain is glucose, a low carbohydrate diet deprives the brain of this energy. This forces the body to use fat to make fuel for the brain. Ketone bodies, including acetone, acetoacetate, and beta-hydroxybutyrate, are produced from fat in the liver. Beta-hydroxybutyrate is found in the highest levels in blood during ketosis (96958,96963,96968,96972,97653).

Anticachectic effects: In an animal model, ketone bodies inhibited muscle and fat breakdown by directly inhibiting skeletal muscle and adipose tissue degrading proteins (97654).

Anticancer effects: The Warburg theory hypothesizes that switching the main fuel source of certain cancer cells, especially gliomas, from glucose to ketones results in cell death (96957,97654). Reducing glucose availability starves cancer cells in vitro and in animal models, possibly by inhibiting insulin-dependent pathways required by the cancer cells, such as glycolysis or the breakdown of glucose, and inducing apoptosis (96978). Ketone bodies themselves also seem to have neuroprotective effects, potentially protecting healthy cells from malignant transformation and side effects of cytotoxic agents (96978,97654). Although it has been suggested that blood glucose, insulin, and insulin-like growth factor-I (IGF-I) levels decrease in cancer patients on the ketogenic diet, meta-analyses of clinical research show that following a ketogenic diet does not affect insulin levels. Any effect on glucose or IGF-I levels is unclear due to inconsistent findings (110203,110208). Any potential clinical impact is unclear; however, most case studies suggest a benefit with respect to tumor response and reduced cancer growth (96957,97654,100845).

Antiseizure effects: The ketogenic diet results in increased ketone bodies in the blood, similarly to

fasting, which has a long history of use for the treatment of epilepsy (96972,96979). The mechanisms of how the ketogenic diet reduces seizure are not completely understood but are likely related to the ketone bodies produced (98417,96968). The ketone bodies, acetone, acetoacetate, and beta-hydroxybutyrate have shown anti-seizure effects in animal models (96968,96972,96974). The ketone bodies reduce neuronal excitability (96972). Possible mechanisms of action of ketone bodies include changes in neurotransmitter systems, altered behavior of channels in the neuronal membranes, improved mitochondrial function, and changes in the activity of histone deacetylases, enzymes involved in gene regulation (98417,96968,96974,97653). Ketone bodies also have antioxidant and anti-inflammatory effects (98417,96968,96974,97653).

The production of ketone bodies is unlikely to completely explain the anticonvulsant effects of the ketogenic diet. Ketone bodies have not had anticonvulsant effects in all animal models (96973). Some ketogenic diets contain caprylic acid and capric acid, medium chain fats. These fatty acids are absorbed directly into the blood and can be used as energy and metabolized to ketone bodies (96973). Furthermore, like ketone bodies, medium chain fatty acids can also be used by the brain as energy (96973). Medium chain fatty acids have anticonvulsant effects in animal models. Mechanisms of action include blocking receptors involved in seizure activity, increasing levels of tryptophan in the brain, and increasing mitochondrial activity (96968,96973).

Metabolic effects: There is interest in the ketogenic diet for altering metabolic parameters during exercise and in metabolic conditions such as diabetes. In a small study, trained male athletes consuming a ketogenic diet for 4 weeks experienced increased fat and decreased carbohydrate utilization during an incremental cycling test exercise. However, increased fat utilization was not prominent in female athletes during the same exercise (102108). The effect of the ketogenic diet on body composition when combined with exercise is unclear. Some individual research shows that consuming the ketogenic diet for 8 weeks in addition to resistance training decreases fat mass and visceral adipose tissue, but does not affect lean body mass, when compared to baseline (102112). However, meta-analyses of clinical research in trained adults shows that following a low-carbohydrate high-fat ketogenic diet for 3-12 weeks while undergoing concurrent training does not affect lean mass, body fat, or body mass, when compared with concurrent training with other dietary strategies (110199,110201). Clinical research in untrained healthy adults undergoing exercise testing after following a ketogenic diet for 3 days shows lower carbohydrate oxidation, higher fat oxidation, and higher serum free fatty acid levels at rest, during exercise, and during recovery from exercise when compared with a mixed diet (113882).

There is interest in whether the ketogenic diet can prevent beta-cell dysfunction which may be precipitated by abnormal proinsulin and testosterone levels. A small clinical study in obese males with low testosterone levels shows that following a very low-calorie ketogenic diet for 12 weeks results in weight loss and normalized levels of blood glucose, insulin, proinsulin, and testosterone when compared with baseline (105654).

A change in thyroid function may play a role in the metabolic effects of the ketogenic diet. Two small clinical trials in healthy adults shows that the ketogenic diet reduces levels of free triiodothyronine when compared with a high carbohydrate, low-fat diet or mixed diet (110195,113882).

Motor function effects: In animal models of spinal cord injury, amyotrophic lateral sclerosis (ALS), or neurological disorders, the ketogenic diet improves motor function. Possible mechanisms of action include improvements in synaptic morphology or changes in nerve synapse function related to ion channels, glutamatergic transmission, or cycling of the vesicles at the synapses. The ketogenic diet improvements in mitochondrial function are thought to play a role (96976). Furthermore, a preliminary clinical study in patients with ovarian or endometrial cancer shows that following the ketogenic diet

for 12 weeks improves physical function when compared with a high-fiber, low-fat diet (102107).

Neuroprotective effects: Animal research suggests that the ketogenic diet protects against Alzheimer's disease. The ketone beta-hydroxybutyrate protects neurons from amyloid toxicity in vitro. Also, in an amyloid animal model, the ketogenic diet improves motor function. Both ketones and medium chain fatty acids inhibit receptors involved in neuronal toxicity and improve mitochondrial function. The ketone beta-hydroxybutyrate inhibits histone deacetylases, involved in gene regulation, reducing oxidative stress. Also, the anti-inflammatory effects of beta-hydroxybutyrate are thought to play a role in the neuroprotective effects of the ketogenic diet (96973,96975).

Weight loss effects: The mechanism of action related to the weight loss effects of a ketogenic diet is likely multi-factorial. It is hypothesized that initial weight loss is related to natriuresis due to ketonuria and glycogen depletion (105896). Additionally, most ketogenic diets used in clinical trials are higher in protein and low in overall energy. It is possible that this diet causes an increase in resting energy expenditure; however, this has not been shown in all studies (96963,96977). Other evidence suggests that eating a ketogenic diet reduces the appetite due to a higher satiety effect (96963,97655). This is possibly related to effects on appetite control hormones or to direct effects of the ketone bodies (96963). Many ketogenic weight loss diets are high in protein. Protein is also satiating, and intake preserves muscle mass during weight loss (96963). However not all research agrees. One small study in patients with ovarian or endometrial cancer shows that the ketogenic diet does not affect satiety when compared with a control low-fat and high-fiber diet, but it does reduce cravings for starch and fast food fats, and it also increases salt cravings (102107). Finally, ketogenic diets seem to reduce lipogenesis, or the production of fats, and induce lipolysis, or fat breakdown (96963).

References

See Monograph References