

## EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- Describe the components and mechanisms of the ketogenic diet for medical purposes.
- List disease states in which the ketogenic diet has been proven to help.
- Use this information to counsel patients who are interested in the ketogenic diet's medical benefits.

After completing the continuing education activity, pharmacy technicians will be able to

- Describe the components of the ketogenic diet for medical purposes
- List disease states in which the ketogenic diet has been proven to help
- Identify situations in which patients need referral for additional information



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### Patient Safety Ketogenic Diet: Fad Weight Loss or True Medical Benefits?

**ABSTRACT:** The ketogenic diet, despite its current popularity, was initially developed to address seizure disorders. Its reliance on high fat, moderate protein, and low carbohydrate intake can make it a challenge for patient adherence. By maintaining a constant state of ketogenesis from eating fatty foods, patients on the ketogenic diet change their natural fuel source from glucose to ketone bodies. Its medical uses include obesity, glaucoma, diabetes, seizures, and other neurodegenerative disorders. A key concept is that patients must strive for ketosis (not ketoacidosis) and monitor medical conditions closely. It is contraindicated in patients with liver failure, pancreatitis, inborn disorders of fat metabolism, primary carnitine deficiency, carnitine palmitoyl transferase deficiency, carnitine translocase deficiency, porphyria, and pyruvate kinase deficiency. People who have type 1 diabetes or who are pregnant should not follow this diet. Some people develop the “keto-flu,” a slang term for symptoms indicative of carbohydrate withdrawal. Numerous reliable resources are available for patients and healthcare providers.

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## INTRODUCTION

Did you know that the ketogenic diet was NOT initially created for weight loss? Recently, the “keto” diet has become another fad diet for people trying to lose weight. Since 2000, more researchers have started to study the ketogenic diet, causing an increase in dieters who are employing this diet.<sup>1</sup>

For decades, various entities have promoted fad diets as a way to lose weight and accrue other health benefits, with no data to back them up. The ketogenic diet

began to reach the public's consciousness in the 1970s, gained popularity in the early 2010s, and by 2017, it was a frequent topic in national news media. Google searches for the ketogenic diet (sometimes called the paleo diet, which is similar but not identical) quadrupled that year; questions about this diet were in the top 10 health questions.<sup>2</sup> Many people started using the ketogenic diet without understanding how it works or its associated benefits and risks. In 2014, celebrities like LeBron James, Kim Kardashian, and Megan Fox used the ketogenic diet during its fad weight loss phase. In 2020, around 6% of Americans were consuming a ketogenic, high fat diet.<sup>3</sup>

In the 1920s, researchers noticed that some patients with epilepsy experienced benefits during fasting, so they discovered a way to mimic fasting to treat the disease.<sup>1</sup> Soon, physicians began to use the ketogenic diet for its antiepileptic properties.<sup>1</sup> However, in the next decades, researchers introduced antiepileptic medications and the ketogenic diet's popularity faded. Treatment for epilepsy still includes some of the first antiepileptic medications: phenobarbital and phenytoin.<sup>4</sup> Although physicians began using phenobarbital in 1912 for epilepsy, the U.S. Food and Drug Administration did not approve phenytoin for use in epilepsy until 1938.<sup>5</sup> In the 1940s, clinicians used troxidone, but its toxicity profile was unacceptable. Ethosuximide, approved in 1958, replaced it. Approval of carbamazepine and valproic acid in the 1960s made the ketogenic diet unnecessary and obsolete for the most part.<sup>5</sup>

Although pharmacists are the medication experts on the clinical team, they must understand all types of treatment, including nonpharmacologic interventions. During a ketogenic diet, patients eat a limited number of carbohydrates so the body will enter ketosis. Because of the diet's intensity, pharmacists and technicians need to understand how the diet works to ensure patient safety. When patients start or are on the ketogenic diet, pharmacists need to counsel patients to ensure no drug interactions occur. Pharmacists also need to counsel patients who may have started the diet by themselves about its benefits and the risks. Also, remember interested dieters might embrace a New Year's resolution regarding ketogenic dieting, because National Keto Day is January 5th!

This continuing education activity summarizes knowledge of the ketogenic diet, the diet's mechanism and its positive and negative effects, current medical uses for patients with epilepsy, diabetes, polycystic ovary syndrome (PCOS), and others, and recommendations for patient education and counseling.

## KETOGENIC DIET

The ketogenic diet alters how the body burns energy, from carbohydrates to lipids. The traditional food pyramid places fats in the smallest section at the top, with carbohydrates in the largest bottom section. The ketogenic diet flips the pyramid, so most recommended foods are fats and very few are carbohydrates.

According to the Dietary Guidelines for Americans, 25% to 35% of an adult's diet should come from fats, 45% to 65% from carbohydrates, and 10% to 30% from protein.<sup>6</sup> In a 2000 calorie day for ketogenic diet patients, fat should account for 70% to 80% or 165 g of daily caloric intake.<sup>7</sup>

Although an exact timeframe is unknown, researchers believe that it can take the body up to four weeks to adapt to the ketogenic diet and ketosis.<sup>8</sup> Patients initiating the diet could try daily exercise to force the body to break down fats, but its efficacy for reducing time to ketosis is unknown.<sup>8</sup>

## Ketogenesis

The ketogenic diet uses ketosis and ketogenesis. When people eat carbohydrates, the body uses cellular respiration to produce energy from breaking down glucose molecules. However, if no carbohydrates are available, which would be the case during extended exercise or fasting periods, the body will naturally enter ketosis. Ketosis is a state of elevated ketone bodies, which include beta-hydroxybutyric acid, acetoacetic acid, and acetone in the blood.<sup>9</sup> When the body needs energy, ketogenesis occurs to produce these ketone bodies, which can be used as an alternative energy source.

In normal cellular respiration, acetyl-CoA is condensed with oxaloacetate to begin the citric acid cycle. Beta-oxidation of fatty acids can produce acetyl-CoA, similar to the production of acetyl-CoA from glycolysis of glucose. In times of reduced glucose (i.e., fasting, extended exercise, ketogenic diet), the body diverts the acetyl-CoA produced from the fatty acids into ketogenesis.

Ketosis begins with fatty acid oxidation and the production of acetyl-CoA. Using the enzyme 3-ketothiolase, acetyl-CoA is converted into acetoacetyl-CoA. Then, the enzyme HMG-CoA synthase converts acetoacetyl-CoA to HMG-CoA.<sup>9</sup> Low glucose levels during starvation or a high fat diet—a signal that the body needs to produce an alternative energy source for the brain—trigger this step of ketogenesis.<sup>10</sup>

The last step of energy production during ketosis is the conversion of HMG-CoA to the ketone bodies acetoacetate (AcAc) and 3-beta-hydroxybutyrate (3HB). Using HMG-CoA lyase, AcAc and 3HB are cleaved from HMG-CoA.<sup>9</sup> By being in a constant state of ketogenesis from eating fatty foods, patients on the ketogenic diet change their natural fuel source from glucose to ketone bodies.

## Ketone Bodies

The 3 main types of ketone bodies are AcAc, 3HB, and least commonly, acetone. The liver produces AcAc, 3HB, and acetone in a 78:20:2 ratio, respectively, during fatty acid oxidation.<sup>11</sup> Acetone is produced the least because it's the byproduct of the uncommon and spontaneous decarboxylation of 3HB.<sup>11</sup> Ketone bodies are the only non-glucose derived energy source for the brain.<sup>10</sup>

**Table 1. Food Options Commonly Used in the Ketogenic Diet<sup>14</sup>**

Fish and seafood	<ul style="list-style-type: none"><li>● Full of protein</li><li>● No carbs</li><li>● Associated with positive cardiovascular and health benefits</li></ul>
Poultry and meat (Chicken, beef)	<ul style="list-style-type: none"><li>● Rich in protein</li><li>● No carbs</li><li>● Limit processed meats</li></ul>
Nuts (Almonds, walnuts, pecans, cashews)	<ul style="list-style-type: none"><li>● High in fiber, protein, and unsaturated fats</li><li>● Very low carbs</li><li>● Antioxidants</li></ul>
Non-starchy vegetables (Broccoli, green beans, bell peppers)	<ul style="list-style-type: none"><li>● Include other vitamins and nutrients</li><li>● Antioxidants</li></ul>
Cheese	<ul style="list-style-type: none"><li>● No carbohydrates</li><li>● High in fats, protein, calcium</li><li>● Too many saturated fats</li></ul>
Avocados	<ul style="list-style-type: none"><li>● Potassium, unsaturated fats</li><li>● Most carbohydrates in avocados are fiber</li></ul>

The brain cannot process fatty acids, so they must be converted into ketone bodies first. They provide energy to the brain because both AcAc and 3HB can diffuse across blood brain barrier.<sup>9</sup>

During a normal day, ketone bodies account for only 2% to 6% of an individual's energy requirements. However, after a three- to four-day fast, ketone bodies account for 30% to 40% of the body's energy source.<sup>9</sup> The liver can produce 185 grams of ketone bodies daily, which is enough to satisfy a person's daily energy needs.<sup>9</sup>

By using ketone bodies, patients can avoid breaking down carbohydrates as an energy source, similar to how the body naturally functions during fasting. Ketone bodies are thought to have a direct beneficial mechanism, which will be discussed later, in disorders like epilepsy.

### Effects of Insulin and Glucagon

Insulin and glucagon are important in ketosis and ketone bodies. Low insulin levels trigger steps in the ketosis process. Insulin, also called the antiketogenic hormone, decreases 3HB production, whereas glucagon, the ketogenic hormone, increases 3HB production.<sup>12</sup>

When humans consume carbohydrates and blood glucose levels rise, the pancreas releases insulin to absorb the blood sugar for energy storage.<sup>13</sup> Insulin inhibits hormone-sensitive lipase and HMG-CoA synthase, enzymes that take part in fatty acid breakdown. It also stimulates acetyl-CoA carboxylase, causing the conversion of acetyl-CoA to malonyl-CoA, and blocking fatty acid transport into the mitochondria.<sup>10</sup> As a result, insulin decreases the need for fatty acid oxidation and ketone bodies are decreased. The ketogenic diet requires patients to avoid carbohydrates to diminish insulin production and promote these mechanisms.

Glucagon does the opposite of insulin. The body uses epinephrine and glucagon to stimulate adipose (fat) tissue to produce more fatty acid.<sup>9</sup> Glucagon triggers phosphorylation of hormone-sensitive lipase and HMG-CoA synthase, thus promoting ketogenesis.<sup>9</sup> The body releases fatty acids from triglycerides, so they can be broken down by the newly activated enzymes.

A successful ketogenic diet requires a high glucagon/insulin ratio, similar to that experienced during fasting and by patients with diabetes. The high ratio increases fatty acid production and oxidation. Ketogenesis will follow.

### Foods Consumed

Most foods for a ketogenic diet will have moderate amounts of proteins, no carbohydrates, with many fats. To prevent heart disease, physicians and pharmacists can counsel patients to eat healthy fats. **Table 1** describes some examples of foods that are common in the ketogenic diet.

Patients on the ketogenic diet must understand how to track their nutrition to diet properly, calculating proteins, carbohydrates, and fats daily. Patients must calculate carbohydrates to account for dietary fiber because fiber is not digested with other carbohydrates.<sup>14</sup> When tracking nutrition, patients on the ketogenic diet must track net carbohydrates, which can be found by subtracting the dietary fiber content from the total carbohydrates. The total carbohydrate level reported on nutrition labels does not accurately reflect the carbohydrate content the patient has consumed.

Most of the foods mentioned in Table 1 are high in fat. Fish, seafood, meat, poultry, and eggs are main staples. Processed meats, like bacon, should be eaten more sparingly compared to non-processed meats, like chicken and beef.<sup>14</sup> Patients can eat chicken and fish more frequently because they promote cardiovascu-

lar health, unlike red meat. Many people believe that berries are not allowed on the ketogenic diet, but strawberries, raspberries, and blackberries have very low net carbohydrates. The total carbohydrates in berries may appear high, but their high fiber content allows berries to have a low net carbohydrate content.

A vegetarian ketogenic diet is a possibility, even though options are more limited. Vegetarian options with high protein and low carbohydrates include nuts, tofu, and seitan (a meat substitute made from the gluten in wheat).<sup>15</sup> These dieters can also enjoy peanut butter-based desserts for more proteins. Seeds are high in fat and have high dietary fiber. For higher calorie meals, eggs and dairy (hard cheeses and plain yogurt) are an important fat option. Eggs have many fats, but essentially no carbohydrates.<sup>15</sup>

Any food that is high in net carbohydrates will disrupt the body's ketosis. These are foods like starchy vegetables, juices, syrup, chips, and crackers.<sup>14</sup> Foods high in carbohydrates will give the body enough energy to not oxidize fatty acids and prevent the production of ketone bodies.<sup>14</sup>

## A KETOGENIC DIET: WHO BENEFITS?

### Obesity

Obesity, a leading risk factor for many chronic health conditions, continues to rise in the United States. According to the CDC, the prevalence of diabetes has increased to 41.9% from 2017 to 2020.<sup>16</sup> Many have adopted low-carbohydrate, high fat lifestyles to lose weight. A 2016 meta-analysis of 11 randomized control trials assessed the efficacy of the ketogenic diet. Among the 1369 participants, those on the ketogenic diet experienced greater weight loss than those who participated in a low-fat diet.<sup>17</sup> After six months to two years of intervention, patients experienced significant weight loss, HDL cholesterol increase, and triacylglycerol (TAG) reduction. The studies were limited by moderate to high heterogeneity and possible publication bias. A 2021 study evaluated the efficacy of the ketogenic diet using a mobile health application in comparison to a calorie restricted, low-fat application.<sup>18</sup> Of the 155 participants, those using the ketogenic diet app experienced greater weight loss (12.3 pounds) at 12 weeks. Hemoglobin A1c (HbA1c) and liver enzymes also improved for the ketogenic diet group. This study was limited by operating fully remotely via the application. Patients could have benefited from in-person counseling or on-site visits to promote adherence.<sup>18</sup>

Another meta-analysis of 13 randomized controlled trials showed that participants on the ketogenic diet benefited from greater weight loss than those on a low-fat diet proving that the ketogenic diet can be used for obese patients. The low-fat diet group consisted of 787 patients while the ketogenic diet group consisted of 790. Patients that were part of the keto group lost approximately 3.6 pounds (1.6 kilograms) more than the low-fat group.<sup>19</sup>

**PAUSE AND PONDER:** Would a fasting patient reach ketosis quicker than a patient who is not fasting?

Patients saw a greater increase in HDL and a more significant reduction in TAG in the keto group.

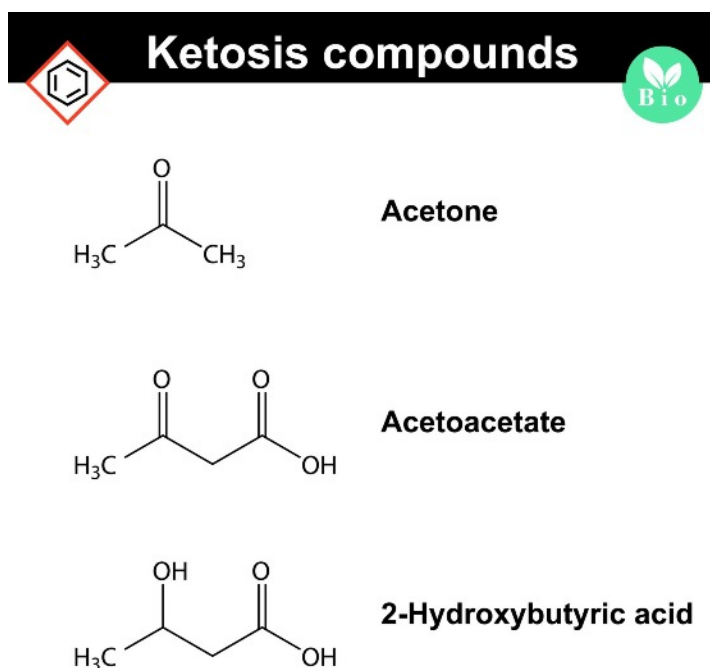
### Type 2 Diabetes

Patients with type 2 diabetes (T2D) sometimes benefit from the ketogenic diet through improved glycemia and reduced insulin resistance. A study of 28 patients with T2D following a ketogenic diet showed that blood glucose and HbA1c improved. The ketogenic diet could potentially help patients with T2D reduce the number or dose of medications.<sup>20</sup> Another comparative study showed that obese patients with T2D had improvement in blood glucose profiles, insulin sensitivity, and HbA1c when adhering to the ketogenic diet for two consecutive weeks.<sup>21</sup> However, the study was limited by short duration and small sample size.

### Polycystic Ovary Syndrome

Similar benefits seem to apply to patients with polycystic ovarian syndrome (PCOS). Patients with PCOS experience hyperandrogenism, insulin resistance, and ovulatory dysfunction.<sup>22</sup> Current treatment options include metformin, clomiphene, and letrozole; the ketogenic diet may provide good results for these women through insulin reduction.

In addition to the symptoms listed above, women with PCOS tend to gain weight, develop acne, and experience hirsutism.<sup>23</sup> Physicians recommend lifestyle modifications and hormonal contraceptives as first line interventions, but often, these interventions are insufficient, and symptoms persist.<sup>23</sup>



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Researchers have conducted many studies to evaluate the benefits of the ketogenic diet for women with PCOS, yet the studies are greatly limited by sample size. For example, a 2019 study consisting of 14 women with PCOS struggling with their weight assessed changes in body weight, BMI, fat body mass, lean body mass, HDL, and several other parameters. At 12 weeks, participants saw a 9.43-kilogram (20.7 pound) reduction in body weight, 3.35 reduction in BMI, and an 8.29-kilogram (18.2 pound) reduction in fat body mass.<sup>23</sup>

A pilot study consisting of five women tested the ability of the ketogenic diet to reduce PCOS symptoms. Researchers provided the women with low-carbohydrate diet books and handouts alongside group meetings to test the ketogenic diet's efficacy for PCOS. Participants consumed fewer than 20 grams of carbohydrates per day for six months. To test participants' adherence, researchers measured ketones and body weight. Throughout the 24-week period, participants lost weight with a mean BMI decrease of four kilograms (approximately 8.8 pounds) which was a 14.3% total reduction in body weight.<sup>24</sup> The study resulted with clear reductions in testosterone, fasting serum insulin, and an overall improvement of PCOS symptoms.

Additionally, an eight-week crossover study involving 30 women with PCOS demonstrated various benefits. On average, weight loss ranged from 1.3 to 1.6 kg (2.8-3.5 pounds). When compared to baseline, the results of this study highlight the relationship between decreases in testosterone and fasting insulin.<sup>25</sup> Overall, improvements in insulin resistance, testosterone levels, and weight loss, the ketogenic diet may help patients with PCOS.

## Epilepsy

The original use for the ketogenic diet was as an antiepileptic therapy in children.<sup>1</sup> After the discovery of antiepileptic medications, the need for the ketogenic diet diminished. However, researchers are bringing the ketogenic diet back to help treat patients who are refractory to modern antiepileptic medications. In combination with medications, researchers have seen up to a 50% reduction in the number of seizures patients are having, with 10% to 15% becoming seizure free.<sup>26</sup> Co-administration with antiepileptics is possible for some medications. However, most patients are children and maintaining this strict diet is difficult.

During a retrospective study, researchers compared the effects of the ketogenic diet to modern anticonvulsant medications in 150 children. At one year, 55% of patients remained on the diet, and 27% of the patients who remained in the trial had a greater than 90% decrease in seizure frequency.<sup>27</sup> The diet allowed children to reduce their medication burden (patients averaged having 6.2 anticonvulsant medications before the trial), and proved to be more effective than many medications. More studies in larger patient populations are needed over longer periods of time to make stronger conclusions.

Research attributes the ketogenic diet's anticonvulsant properties to an increased seizure threshold. Mitochondria in the brain have healthier biogenesis and density, leading to increased resistance to metabolic stress.<sup>28</sup> Another way the diet increases seizure threshold is through decreased glucose consumption and production of glycolytic ATP.<sup>28</sup> Subsequently, potassium channels remain open and hyperpolarize the neuronal membrane.<sup>28</sup>

Researchers have found that ketone bodies produced from fatty acid oxidation have their own anticonvulsant effects. Although different ketone bodies have different effects, researchers have found that they can alter various neuronal membrane transporters to decrease excitability. Ketone bodies can inhibit transporters like the vesicular glutamate transporter and neuronal potassium channels. Inhibition of these transporters prevents signal transmission and causes decreased excitability of neuronal cells.<sup>29</sup>

## Neurodegenerative Disorders

In addition to epilepsy, promising evidence shows that the ketogenic diet has favorable effects for some neurodegenerative disorders. As the incidence of Alzheimer's disease (AD) increases, few treatment options are available. The ketogenic diet may reduce deposition of amyloid beta (A $\beta$ ) plaques in patients with AD. With the addition of D- $\beta$ -hydroxybutyrate (an enantiomer of the ketone body 3HB) to the ketogenic diet, ketones were able to increase neuron survival by reversing A $\beta$  (1-42) toxicity.<sup>30</sup> By increasing ketone production in the liver, the ketogenic diet can reduce the production of reactive oxygen species.<sup>31</sup> Ketone bodies also work to block histone hyper-acetylation initiated by histone deacetylases (HDACs), increasing antioxidant levels. The ketogenic diet can improve metabolic efficiency which improves ATP concentrations resulting in further protective effects.<sup>31</sup> Ketones' neuroprotective effects can potentially help patients with Parkinson's disease by reducing oxidative stress, maintaining energy supply, and modulating deacetylation and inflammatory responses.<sup>31,32</sup> Because they can reduce inflammation and inhibit the glutamate excitatory synapse, infusions of ketone bodies like 3HB may lead to small improvements in Parkinson's symptoms.<sup>32</sup> The use of the ketogenic diet for Parkinson's is still controversial, thus further research is necessary.

## Glaucoma

Glaucoma is the second leading cause of vision loss in the world.<sup>33</sup> Because ketone bodies are the major source of energy when participating in the ketogenic diet, mitochondrial dysfunction in the retina and optic nerves associated with glaucoma may be decreased.<sup>32,34</sup> A 2020 observational study assessed the benefit of the ketogenic diet in 185,638 adults with glaucoma from three studies between 1976 and 2017. Results showed that following a low carbohydrate diet was associated with 20% lower risk of developing primary open-angle glaucoma with initial para-central visual field loss.<sup>35</sup> However, evidence is still lacking, and researchers need to investigate more to prove the ketogenic diet's efficacy for glaucoma.



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## Colorectal Cancer

According to the American Cancer Society, colorectal cancer is the third leading cause of cancer-related deaths in men and women in the United States.<sup>36</sup> A 2022 study suggests that the ketone body, 3HB, can suppress colorectal cancer.<sup>37</sup> In one experiment, investigators evaluated the ability of the ketogenic diet to prevent tumor growth and development in mice.

They discovered that 3HB could suppress tumor growth by reducing proliferation of colonic crypt cells.<sup>37</sup> 3HB induced positive changes in tumor growth through the upregulation of the homeodomain-only protein X (HOPX). The HOPX protein inhibits cancer organoid growth when overexpressed.<sup>37</sup> Mice fed the ketogenic diet showed elevated levels of HOPX specific to the colonic tissue.

Overall, mice assigned to the ketogenic diet experienced improved long-term survival rates. To test the efficacy of the ketogenic diet for existing tumors, after two cycles of dextran sodium sulfate, researchers introduced the diet to the mice. After exposure to the diet, tumor growth decreased. When researchers discontinued the ketogenic diet from the mice, tumor development proceeded.<sup>37</sup>

This discovery led to further testing, this time in human organoids. Organoids are tissue cultures derived from stem cells.<sup>38</sup> In the right environment, they are used to replicate organs. They are an essential tool to monitor disease development. Findings mimicked the results from the mice in 41 patients with colorectal cancer. This suggests that the ketogenic diet may be used for the prevention and treatment of colorectal cancer in the future.<sup>37</sup>

**PAUSE AND PONDER:** How do you think patients will feel using the ketogenic diet as a primary treatment for neurodegenerative diseases in the future?

## Contraindications to the Ketogenic Diet

Some patients should not follow the ketogenic diet. It is contraindicated in patients with liver failure, pancreatitis, inborn disorders of fat metabolism, primary carnitine deficiency, carnitine palmitoyl transferase deficiency, carnitine translocase deficiency, porphyria, and pyruvate kinase deficiency.<sup>39,40</sup>

Because of the high risk of developing diabetic ketoacidosis (DKA), patients with type 1 diabetes on SGLT2 inhibitors should not participate in the ketogenic diet.<sup>41</sup> DKA occurs when the body produces a dangerously high level of ketones at a rapid pace. Feeling extremely thirsty and frequent urination are early symptoms of DKA. Later symptoms of DKA include dry skin and mouth, flushing, fatigue, stomach upset, and pain. Another notable warning sign of DKA is a fruity odor on the patient's breath. Acetone is responsible for the sweet scent and indicates high levels of ketones in the body.<sup>42</sup> If left untreated, DKA can further develop, ultimately leading to death.

Pregnancy is also a contraindication. The CDC recommends 340 additional calories per day during the second trimester of pregnancy and 450 additional calories per day during the third trimester.<sup>43</sup> The CDC also recommends a well-balanced diet for women who are expecting. Losing weight during pregnancy is not safe and can be harmful to a patient's baby.<sup>43</sup> Folic acid and iron supplementation is pivotal in a fetus' development. The World Health Organization recommends daily iron and folic acid supplements to reduce the risk of low birth weight.<sup>44</sup> If a pregnant woman were to go on the ketogenic diet, she would need to ensure she consumes the suggested dose of 120 mg elemental iron and 2800 µg (2.8 mg) folic acid daily.<sup>44</sup> Overall, no evidence indicates that the ketogenic diet is safe for pregnant women.

## SAFETY AND COUNSELING

Although several studies suggest the ketogenic diet can be effective for weight loss, limited literature is available concerning its long-term effects. Long-term effects include hepatic steatosis,

hypoproteinemia, kidney stones, and vitamin and mineral deficiencies.<sup>40</sup>

Currently, no guidelines address the ketogenic diet specifically, and other guidelines do not include the ketogenic diet for the treatment of the previously mentioned diseases. Researchers must complete longer term studies with larger patient populations to prove the ketogenic diet’s benefits and elucidate any long-term risks. Pharmacists and other healthcare providers should keep this in mind when recommending the diet to patients.

**The Keto-Flu**

A common adverse effect of the ketogenic diet is the “keto-flu.” The symptoms are indicative of carbohydrate withdrawal that can create symptoms like brain fog, fatigue, nausea, vomiting, constipation, and muscle soreness.<sup>40, 39</sup> Symptoms usually begin within one to two days and resolve within a week or less. Pharmacists can counsel patients on proper hydration, light exercise, rest, and starting the diet slowly to try to prevent the keto-flu.

**Cardiovascular Effects**

As research has previously shown, the ketogenic diet shows short-term benefits for obesity and cholesterol. Due to the over-consumption of fats, researchers wondered about the longer-term effects. In rodent studies, the ketogenic diet led to the development of hepatic inflammation and nonalcoholic fatty liver disease.<sup>45</sup> Limited research has been done for nonalcoholic fatty liver disease in humans and more study is needed.

**Other Adverse Effects**

While on the ketogenic diet, patients may experience constipation. The healthcare team should implement a bowel regimen for the patient including an agent like polyethylene glycol 3350 (MiraLAX®) that’s sugar-free, meaning it adds no additional carbs. Other notable side effects are kidney stones and a decrease in bone density. To prevent kidney stone occurrence, pharmacists can counsel patients on drinking large amounts of liquids. Patients can reach out to their providers to ensure they check bone health routinely. Several advisory groups recommend bone mineral density screening for women aged 65 and older and men aged 70 and older, and for other patients who are at high risk. Patients participating in the ketogenic diet are no exception, and could be considered high-risk if they do not consume enough calcium and vitamin D. Pharmacists can counsel patients to monitor their calcium and vitamin D intake and supplement it if necessary. Upon screening, providers may also recommend calcium and vitamin D supplementation for patients who experience a decline in bone mineral density.<sup>46</sup>

**What Can Health Professionals Do?**

Pharmacists can counsel patients on ketone testing to prevent occurrences of DKA. When a patient’s blood glucose exceeds 240 mg/dL, testing ketone levels every four to six hours is

Table 2. Ketone Levels <sup>48</sup>	
Normal Ketone	≤ 0.5 mmol/L
Nutritional Ketosis	1 - 3 mmol/L
Ketoacidosis	≥ 20 mmol/L

**PAUSE and PONDER:** On average, how long do you think a patient can remain adherent to the ketogenic diet lifestyle?

warranted.<sup>47</sup> Ketones can be monitored through the urine and blood. A urine stick test is the most common and changes color depending on the ketone level. Although urine tests are convenient, blood ketone tests from finger sticks are more accurate because they measure 3HB and/or AcAc in the blood.<sup>48</sup> If ketone tests indicate high levels, the patient is at moderate or high risk for ketoacidosis and patients should seek medical attention. **Table 2** shows normal ketone levels, the optimal state of nutritional ketosis, and the level for ketoacidosis.

Patient adherence to long-term regimens always becomes challenging. Counseling patients on the importance of sticking to their diet and other medications will increase the likelihood of desired results.

Medication management is a vital component of patient safety. To ensure that starting the ketogenic diet is safe, a healthcare professional should perform a complete medication reconciliation. Pharmacists, with an interdisciplinary team, should then develop a plan for medication adjustments (including OTCs) and carbohydrate intake. The use of medication package inserts, institutional databases, and manufacturer helplines can assist the team in determining carbohydrate content of drugs to make the process more seamless.<sup>46</sup> The following oral suspensions contain high carbohydrate contents:<sup>49</sup>

- Amoxicillin
- Nystatin
- Levetiracetam
- Midazolam
- Phenobarbital
- Phenytoin
- Baclofen
- Ibuprofen

Making patients aware that they must inform the healthcare team of any new medications is equally as important.



Some medications are of concern with the ketogenic diet.

- Patients taking SGLT2 inhibitors should not participate in nutritional ketosis due to the increased risk of diabetic ketoacidosis.
- Clinicians need to monitor patients taking the anticonvulsant valproate (a fatty acid) and might need to adjust their doses since the ketogenic diet increases metabolic efficiency and valproate can be burned by cells for energy.<sup>50</sup> Patients may feel as though valproate is not as effective after starting the ketogenic diet. The dose, in this case, may need to be increased temporarily.
- A case study showed that topiramate can increase blood pH, inducing metabolic acidosis and kidney stones.<sup>51</sup> This may become hazardous if patients are already in nutritional ketosis.
- Patients may experience hypotension while taking anti-hypertensive agents and following the ketogenic diet. They should monitor blood pressure frequently.

Pharmacists and other health professionals should inform patients to stay hydrated to reduce the risk for kidney stones and eat low salt food items.

MYTHS AND FACTS

The ketogenic diet has become increasingly popular over the years. Halle Berry, Vanessa Hudgens, Kourtney and Kim Kardashian are a few of many celebrities that have tried the keto-

genic diet and have seen incredible results. MTV’s Jersey Shore star, Vinny Guadagnino, also known as the Keto Guido, is no stranger to the diet and has even written a keto cookbook. Seeing such drastic transformations all over tabloids and social media, without a doubt leaves people wondering “Why not? If they can do it, so can I,” while others think, “This can’t be real.”

Many misconceptions create skepticism among patients from the abundance of information available on the internet. Pharmacists can alleviate patient worries by staying informed and referring patients to reliable resources. [Table 3](#) dispels common myths.

Another common misinterpretation is that any low-carbohydrate food is considered keto. No food item has the same benefit as the other. The healthcare team must work with patients to create dietary plans that are more feasible for them. With a tailored diet plan, patients are more likely to feel structured and reach their goals. Overall, providers should conclude that patient education is necessary to certify patient trust and safety.

PATIENT RESOURCES

Reliable resources for patients are hard to find. [Table 4](#) (next page) describes some resources that pharmacists can provide to patients for more information.

Table 3. Myths and Facts About the Ketogenic Diet <sup>52</sup>	
MYTH	FACT
The ketogenic diet is bad for your health.	The ketogenic diet has several health benefits including: <ul style="list-style-type: none"><li>• Weight loss</li><li>• Improved brain function</li><li>• Reduction of seizures</li><li>• Blood sugar management</li><li>• Improvement of PCOS symptoms</li></ul> Side effects may include nausea, vomiting, constipation, or other common side effects.
All I have to do is consume any type of fat while going keto.	Patients should eat healthy fats like avocados, nuts, seeds, and fish. Healthy fats lower LDL levels and raise HDL levels. Unhealthy fats, saturated and trans fatty acids (e.g., fried foods, pastries, butter, and cream) raise LDL levels.
If I go keto, I will get ketoacidosis.	Ketosis and ketoacidosis are different conditions. The ketogenic diet induces ketosis. <ul style="list-style-type: none"><li>• In ketosis, the body burns fat since carbohydrates are unavailable. Nutritional ketosis is a normal response.</li><li>• Ketoacidosis is a complication seen primarily in patients with T2D where the blood becomes acidic. It can be life-threatening.</li></ul>
I will have no energy if I start a ketogenic diet.	Some people may experience an adjustment period while beginning the ketogenic diet. They may experience temporary fatigue, brain fog, or the “keto-flu.” Eventual ketone production fuels the brain with energy and resolves symptoms.
The ketogenic diet is only useful for weight management.	The ketogenic diet has proven effective in patients with diabetes, PCOS, metabolic syndromes, Alzheimer’s disease, and obesity.
I can’t drink any alcohol while on the ketogenic diet.	Various low-carb alcoholic beverages can be substituted. Light beer, vodka, gin, and rum are a few examples, but patients should keep intake low-moderate. Patients should avoid sweet drinks and cocktails to prevent high sugar intake.



**Table 4. Resources About the Ketogenic Diet for Patients**

Cleveland Health Clinic	<ul style="list-style-type: none"><li>• Discusses what patients eat on the ketogenic diet</li><li>• Small tidbits on benefits and risks</li><li>• Includes information on populations that could benefit from the diet</li><li>• <a href="https://health.clevelandclinic.org/what-is-the-keto-diet-and-should-you-try-it/">https://health.clevelandclinic.org/what-is-the-keto-diet-and-should-you-try-it/</a></li></ul>
Harvard University Health	<ul style="list-style-type: none"><li>• Discusses key takeaways from a ketogenic diet review</li><li>• Gives food examples</li><li>• Easy-to-understand</li><li>• Discusses health implications for certain patient populations</li><li>• <a href="https://www.health.harvard.edu/blog/ketogenic-diet-is-the-ultimate-low-carb-diet-good-for-you-2017072712089">https://www.health.harvard.edu/blog/ketogenic-diet-is-the-ultimate-low-carb-diet-good-for-you-2017072712089</a></li></ul>
Academy of Nutrition and Dietetics	<ul style="list-style-type: none"><li>• Popular nutrition website that presents findings on various health topics</li><li>• Discusses populations that the ketogenic diet would not be safe in</li><li>• Gives background on the diet</li><li>• <a href="https://www.eatright.org/health/wellness/fad-diets/what-is-the-ketogenic-diet">https://www.eatright.org/health/wellness/fad-diets/what-is-the-ketogenic-diet</a></li></ul>
Everyday Health	<ul style="list-style-type: none"><li>• Discusses risks and benefits of the diet</li><li>• Provides food substitutions and daily meal plans</li><li>• Discussion on potential supplements and vitamins that may be beneficial to dieters</li><li>• Discusses other nutrition techniques for other topics</li><li>• Articles are peer-reviewed</li><li>• <a href="https://www.everydayhealth.com/diet-nutrition/ketogenic-diet/comprehensive-ketogenic-diet-food-list-follow/">https://www.everydayhealth.com/diet-nutrition/ketogenic-diet/comprehensive-ketogenic-diet-food-list-follow/</a></li></ul>
EatingWell	<ul style="list-style-type: none"><li>• Brief explanation about the ketogenic diet</li><li>• Provides variety of food options for dieters</li><li>• Easy-to-understand and discusses other nutrition techniques</li><li>• Peer reviewed and gives background on all authors/editors</li><li>• <a href="https://www.eatingwell.com/article/290697/ketogenic-diet-101-a-beginners-guide/">https://www.eatingwell.com/article/290697/ketogenic-diet-101-a-beginners-guide/</a></li></ul>



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## CONCLUSION

Following a low-carbohydrate, high fat diet that uses ketone production to fuel the body requires a large selection of foods if patients are to maintain this diet. This is the challenge of the ketogenic diet. Pharmacists and technicians need a good understanding of what this diet is—and what it is not—so they know when prescribers are likely to use it for diseases. Pharmacists, as they screen for contraindications, should identify the signs of ketosis and counsel patients on managing safe ketone levels.

Patient education is the key to reaching patient goals. Pharmacists must be ready to address patient questions and concerns regarding the ketogenic diet in conjunction with current medications. When pharmacists are a part of the care process, outcomes improve.

**Figure 2** (next page) summarizes key points to improve your practice.

**Figure 1. Safety and Counseling Related to the Ketogenic Diet**

**Best**

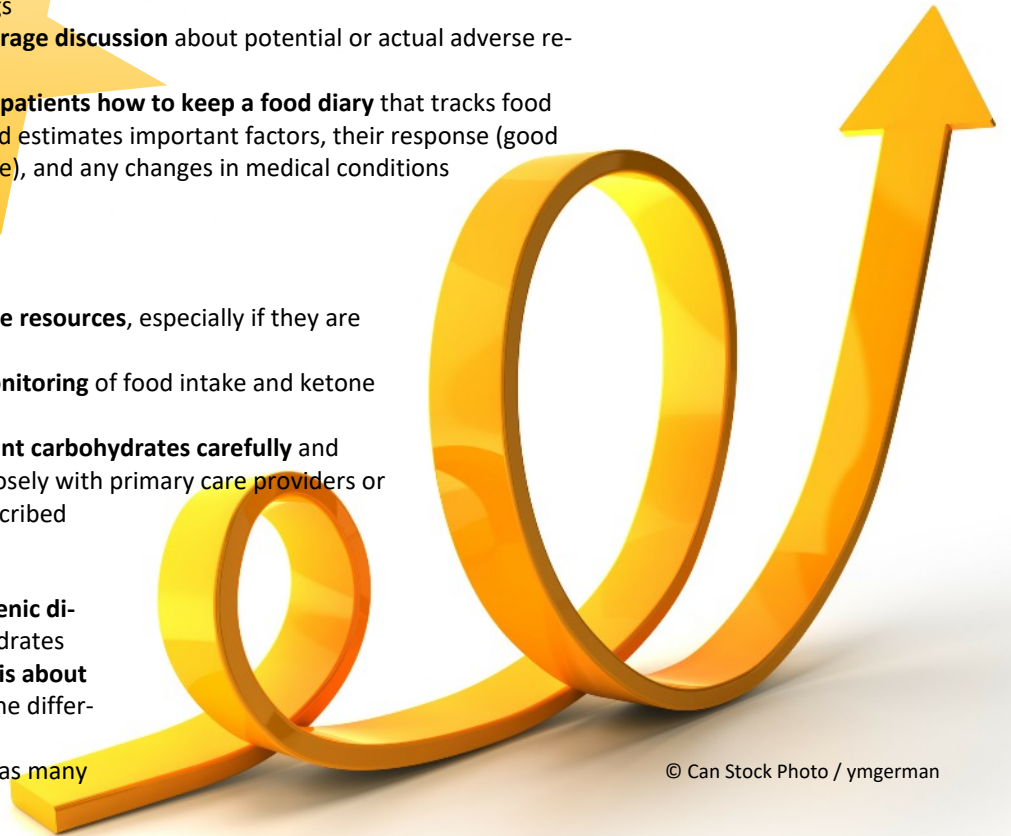
- ① **Be COMMUNITY CHAMPIONS!** Encourage people to talk about their diets and dietary changes! So many foods interact with drugs
- ② **Encourage discussion** about potential or actual adverse reactions
- ③ **Show patients how to keep a food diary** that tracks food intake and estimates important factors, their response (good or adverse), and any changes in medical conditions

**Better**

- ① **Refer patients to reliable resources**, especially if they are using this diet medicinally
- ② **Recommend careful monitoring** of food intake and ketone levels
- ③ **Remind patients to count carbohydrates carefully** and counsel patients to work closely with primary care providers or specialists if the diet is prescribed

**Good**

- ① **Familiarize yourself with the ketogenic diet's rules** concerning fats and carbohydrates
- ② **Remember that the ketogenic diet is about ketosis, not ketoacidosis** and explain the difference to patients
- ③ **No judgment!** The ketogenic diet has many uses



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