

# Overview and Potential Applications of the Ketogenic Diet in Dogs

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## Abbreviations

AD	Alzheimer's disease
BHB	Beta-hydroxybutyrate
DKA	Diabetic ketoacidosis
MCT	Medium-chain triglycerides

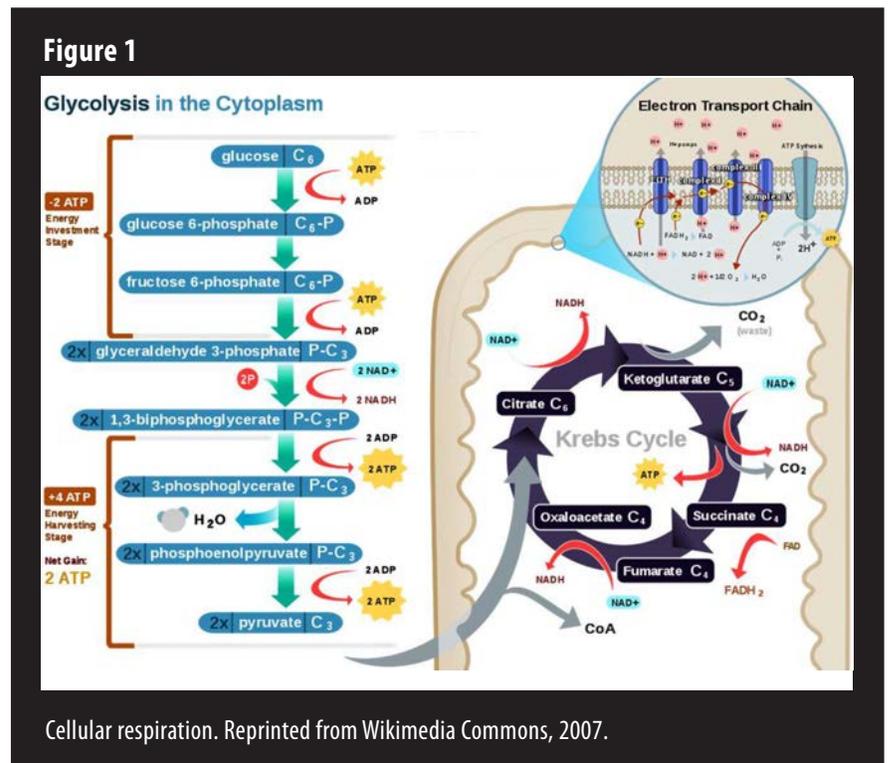
## Abstract

The ketogenic diet is a nutritional strategy that shifts energy metabolism from glucose to fats as the primary fuel source for cells throughout the body. This change leads to the production of ketones in the liver. Ketones can provide an alternative fuel source to glucose for cells in various organs and tissues which have healthy functioning mitochondria, including the brain. Ketogenic therapies have shown potential benefits for numerous chronic disease states in humans, but studies are very limited in dogs.

of its high metabolic demand and obvious necessity for life. In humans, the brain accounts for about 20% of all energy needs, a relatively high amount given its small size (~2% of body mass). While the neurons in the brain can utilize some other energy sources (ie, lactate and small fatty acids), it relies primarily on glucose derived from the intake of dietary carbohydrates as its major source of energy. Glucose is converted into pyruvate and then funneled into the Krebs cycle, which is a key metabolic pathway in cellular respiration (Figure 1). The Krebs cycle takes place

## Introduction

Ketogenic therapies involve nutritional strategies that shift the body's metabolism to a state of significant ketone production (1). Acetone, acetoacetate, and beta-hydroxybutyrate (BHB) are the 3 main ketone bodies produced in mammalian species as a product of fat metabolism in the liver. A state of ketosis can be achieved via severe caloric restriction, by supplementing a current diet with medium-chain triglycerides (MCT), or by feeding a ketogenic diet featuring a higher fat content and severe carbohydrate restriction (1). Consuming a ketogenic diet, which is a biochemical model of fasting, shifts metabolism to the use of fat as the primary fuel source instead of carbohydrates. The body needs constant energy production using the metabolic currency of ATP to maintain life. When discussing energy needs, emphasis is often placed on the brain because

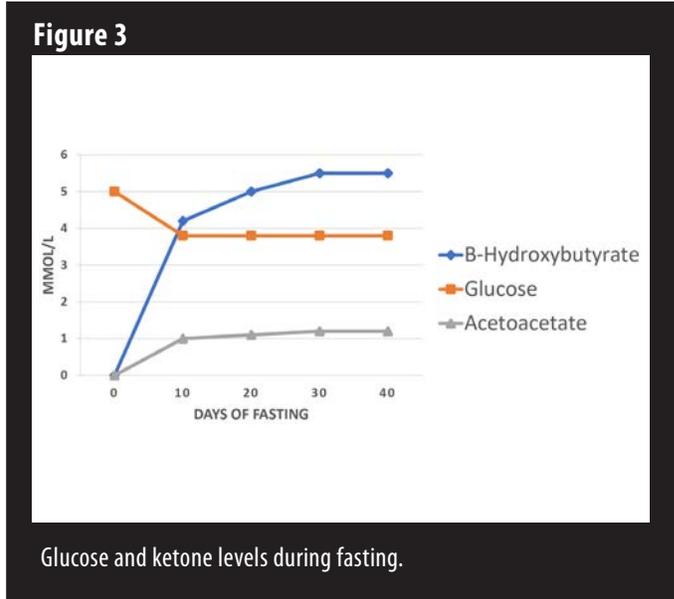
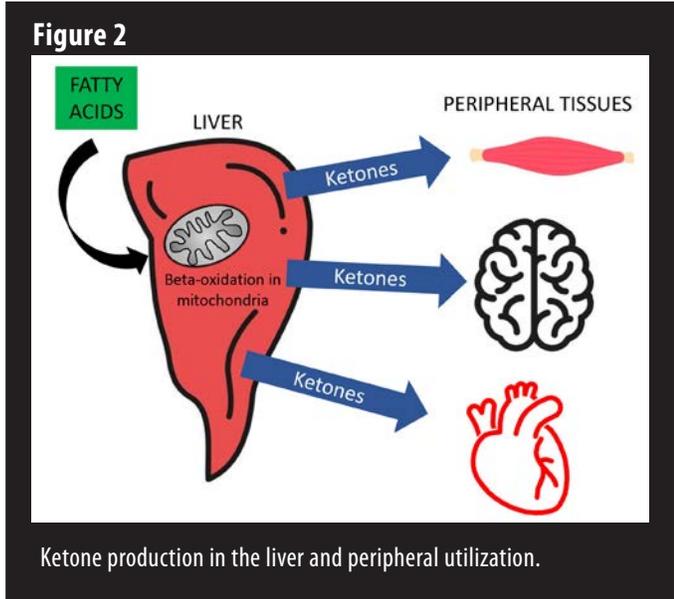


in mitochondria, which generate most cellular energy. During periods of severe calorie or carbohydrate restriction, a limited source of glucose stored in the form of glycogen can be found in the liver. How long this glycogen lasts depends on the size of the storage and energy expenditure demands. Even periods of extreme starvation do not cause death; therefore, the brain must be utilizing an alternative energy source to maintain normal function. After the supply of liver glycogen is exhausted, a hormonal shift occurs. As blood glucose falls, there is a resulting decrease in blood insulin and a rise in glucagon, initiating gluconeogenesis to maintain euglycemia. This hormonal shift promotes lipolysis in the body's fat stores, making the fatty acids available for beta-oxidation in the mitochondria. In this way, fats become a major source of ATP throughout the body (2, 3). In the liver, beta-oxidation does not result in ATP production. Rather, the liver mitochondria metabolize the fatty acids to produce ketone bodies, primarily acetone, acetoacetic acid, and BHB. When the body produces ketones in a sufficient amount (at least 0.3-0.5mmol/L), it is said to be in a state of ketosis. Ketones can readily cross the blood-brain barrier to be used as fuel by neuronal mitochondria along with many other tissues in the body (Figure 2). This process explains why animals (including humans) can go for prolonged periods without any intake of glucose and still survive. To demonstrate that the brain can effectively utilize ketones as a fuel source, a study was performed in which human subjects with high levels of circulating BHB were injected with insulin to lower their blood glucose to dangerous levels, yet remained symptom-free with normal neurologic function (4, 5). In a normal state of ketosis without exogenous insulin, glucose levels will stabilize at around

65 to 70 mg/dL in humans (Figure 3). Anecdotally, the same appears to be true in dogs. This occurs because glycerol, the backbone of triglycerides, is cleaved during the process of ketone production in the liver and is then converted to glycogen, which can be used to make a steady stream of glucose (gluconeogenesis) (6). Glycerol from triglyceride is not the only non-carbohydrate substrate that can be used for gluconeogenesis. Glycogen can also be produced from the breakdown of muscle tissue during periods of fasting or intense exercise (7). The ability for the body to produce ketones is the explanation as to why one can not only survive, but even thrive in the absence of glucose intake.

### Styles of Ketogenic Diets

The main goal of a therapeutic ketogenic diet is to shift the metabolism to utilize primarily fat as the fuel source. There are several nutritional strategies used to enter into a state of nutritional ketosis. The classical 4:1 ketogenic diet, originally designed to help treat childhood epilepsy, is composed of a 4:1 ratio of fat grams to combined grams of protein and carbohydrates. This equates to 90% of the caloric intake coming from fat. Ideally, this ratio is kept consistent to ensure that a person remains in a state of nutritional ketosis; however, individual variations will exist. For all intents and purposes, a state of nutritional ketosis is a binary state; a person or dog is either in it or not. Once the dietary intake of carbohydrates is reduced, the body will utilize glycogen stores in the liver to continue to use glucose as its primary fuel source. As the glycogen stores are depleted, metabolism will shift to ketones and fatty acids as the main energy sources. It is worth noting that only liver glycogen can contribute to the release of glucose into

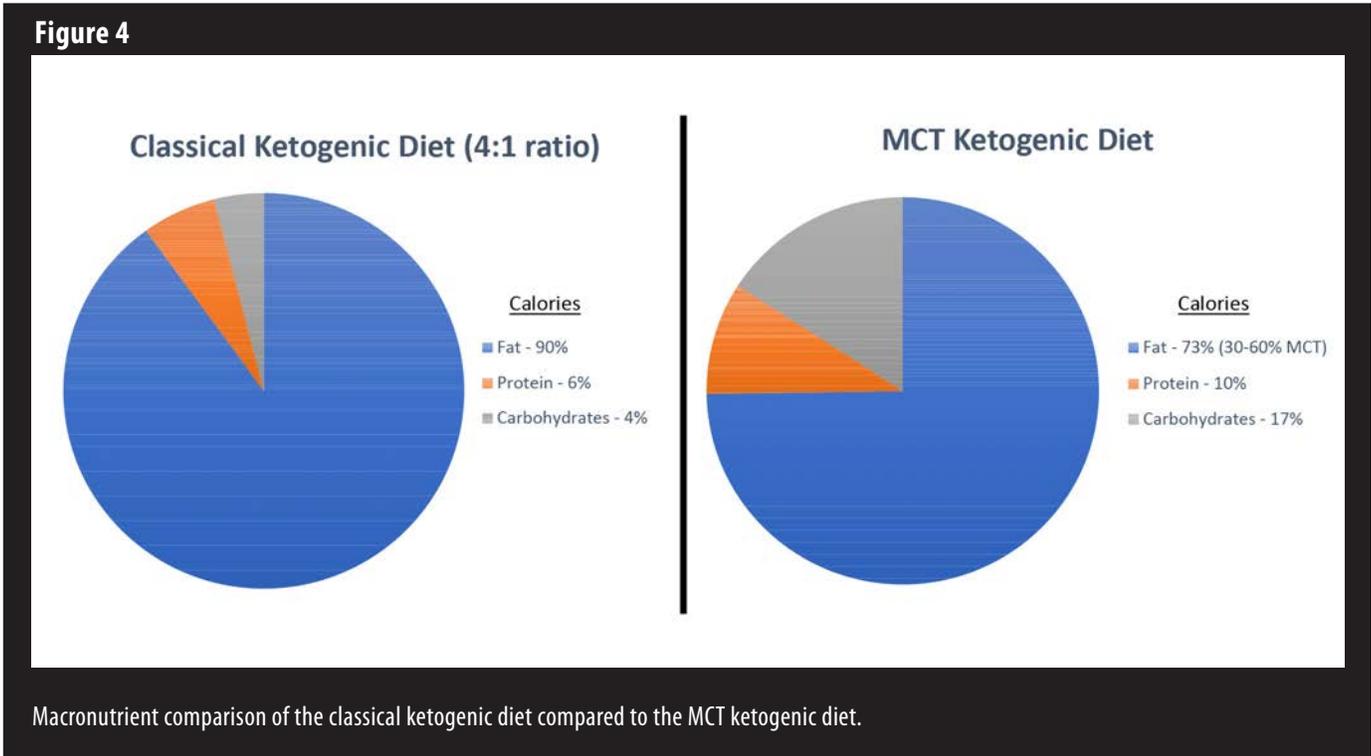


the bloodstream. Muscle glycogen cannot directly contribute to the level of circulating blood sugar because muscle tissue lacks the enzyme glucose-6-phosphatase (8). After refeeding carbohydrates, glycogen stores will be replenished in the liver and metabolism will shift back to using glucose as a primary fuel. This requires that ketogenic dietary plans be followed very strictly. Even a modest amount of carbohydrate or excess protein will prevent a person or dog from entering a state of nutritional ketosis. Due to the high fat content, a slow transition to a ketogenic diet is recommended. If rushed, early gastrointestinal intolerance can often result in poor compliance. For dogs, one can even begin with a ratio of 1:1 (grams of fat to combined grams of protein and carbohydrate) and then gradually work up to a higher ratio if needed. Monitoring blood ketones may demonstrate that a ratio of 1:1 or 2:1 is sufficient. To make the diet more flexible a few modifications can be made, such as using lower-glycemic carbohydrates or by adding MCTs (Figure 4). These are metabolized primarily into ketones, thus allowing a higher percentage of carbohydrate in the diet while maintaining nutritional ketosis (9). Tropical oils, especially coconut oil, are particularly high in MCT. MCTs are fatty acids that contain 6- to 12-carbon chain backbones. They include caproic acid (C6), caprylic acid (C8), capric or decanoic acid (C10), and lauric acid (C12). Because of the shorter chain length of the fatty acids, MCTs are rapidly broken down and absorbed into the body and, unlike longer-chain fatty acids, go straight to the

liver. There they can be used as an instant energy source or turned directly into ketones.

It is also worth discussing the difference between nutritional ketosis and diabetic ketoacidosis (DKA). Nutritional ketosis is a normal physiologic response to low carbohydrate (glucose) intake. DKA occurs in patients with either a complete absence of insulin (Type I) or severe insulin resistance (Type II). With a normally functioning pancreas, even in the absence of external carbohydrate sources, enough insulin is produced so that BHB levels cannot rise above about 5-8 mmol/L, which is well below the level required to induce a pathologic acidotic state. In nutritional ketosis there is low insulin and moderate ketone levels. In a state of DKA, there are very high insulin and ketone levels, and BHB can reach 20-25 mmol/L (Table 1) (10-12). These

Blood Level	Normal Diet	Ketogenic Diet	Diabetic Ketoacidosis
Glucose (mg/dL)	80-120	65-80	>300
Insulin (µU/L)	6-23	6.6-9.4	Near 0
Ketone Bodies (mmol/L)	0.1	7/8	>25
pH	7.4	7.4	<7.3



two metabolic states are completely separate from one another, and the word ketosis should not be associated with the dangerous state of ketoacidosis.

## Therapeutic Applications

Ketone bodies have numerous physiological effects on the body. They can be used as fuel, increase mitochondrial efficiency, upregulate pathways to mitigate oxidative stress, influence post-translational modifications of proteins, act as extracellular signaling ligands, and increase the expression of brain-derived neurotrophic factor (1). Because of these effects, metabolic therapy utilizing a ketogenic diet has many promising applications, including treatment of epilepsy, neurodegenerative diseases, obesity, cardiovascular disease, diabetes, cancer, traumatic brain injury, and stroke (1, 12-20).

While knowledge about the utility and benefits of being in a ketogenic state is growing rapidly, historically the best example of its use is in seizure patients refractory to standard medications. This treatment strategy is not new, and its use can be dated back to ancient Greece (1). Dietary management of epilepsy began to fall out of favor when antiepileptic drugs such as diphenylhydantoin became available in the 1930s (9). While the exact mechanism for how a ketogenic diet helps to prevent seizures is unknown, it is clear that ketones do possess anti-epileptic properties (21). Mechanistic theories include direct and indirect anticonvulsant properties of ketones themselves, decreased production of reactive oxygen species, increased synthesis of GABA (a neurotransmitter in the brain that reduces cellular excitability), reduced glutamate (an excitatory neurotransmitter in the brain), and boosting the production of energy in brain tissue via mitochondrial biogenesis (22-27). A meta-analysis of 16 studies using a ketogenic diet to treat drug-resistant epilepsy in adult humans showed seizure freedom or >50% reduction in seizures in 13% and 53% of participants respectively (28).

Evidence evaluating a ketogenic diet in dogs is very sparse other than anecdotal accounts and a case report (29). Much of what is recommended is extrapolated from what is known in people; however, there are noticeable differences between humans and animals. When fasted, humans will enter into a state of ketosis much more quickly and with considerably higher plasma levels of ketones as compared to dogs (30-32). This is not because dogs are inefficient at ketone production. The differences in plasma ketone levels between dogs and other species after prolonged fasting is a result of enhanced peripheral utilization by extrahepatic tissues in the dog, not because the mitochondria in the liver produce fewer ketones (32). Simply put, dogs are very

efficient at utilizing ketones as energy; therefore, high levels do not accumulate in the plasma.

Due to concerns with palatability and side effects (gastrointestinal tolerability) of a classical 4:1 ketogenic diet, alternative strategies in dogs have centered around feeding a diet supplemented with MCTs to increase the level of ketones while maintaining a reasonable level of carbohydrates. A recent study randomly evaluated the use of an MCT diet in dogs with epilepsy and found a significant seizure reduction compared to the control group (33). It has been proposed that there is a direct anti-seizure effect from the MCT decanoic acid (C10) by inhibition of the alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subunit on glutamate receptors in the brain (26). Glutamate is an excitatory neurotransmitter that plays a major role in the propagation of seizure activity. A ketogenic diet, or one supplemented with MCTs, can be used to supplement a patient's medical regimen, especially for those whose responses have been refractory to treatment with standard anti-epileptic medications. The apparent success with MCT strategies was the essence for the development of a specialty diet (a) which is supplemented with MCT. While this study reported a statistically significant decrease in seizures in dogs fed the MCT diet (2.31 seizures per month) versus when fed the control diet (2.67 per month), this difference is not clinically significant in the least (33). The study also reports a statistically significant increase in BHB concentration in dogs fed the MCT diet (0.041 mmol/L) versus the control diet (0.031 mmol/L). Even if the difference in BHB concentration between the 2 diets is statistically significant, the values are well below those which are anecdotally measured with home-prepared diets (often 0.5-3.0 mmol/L). Having said that, the suggestion of supplementing with MCTs is still logical, but in this author's opinion, a client may have better control of MCT/ketone levels by adding a high quality MCT oil to their dog's current diet and titrating the dose based on gastrointestinal tolerability.

While the most common therapeutic application of a ketogenic diet is for seizures, many other disease states have shown benefit. Dogs with idiopathic epilepsy are known to have a higher frequency of behavioral disorders including aggression, trainability, attention problems, and excitability (34). In 2015, a randomized, placebo-controlled, double-blinded study evaluated the effects of MCT supplementation in dogs with idiopathic epilepsy that were displaying attention deficit hyperactivity disorder (ADHD)-like behavior. In addition to a significant reduction in seizure frequency, there was also a significant reduction in attention deficit-related symptoms and stranger-directed fear. While the exact mechanism for the behavior improvement is not

known, it is suggested to be secondary to changes in energy metabolism in the brain (35).

The ketogenic diet may also have a role in treating cancer. This line of thinking supports the metabolic theory of cancer being a result of altered cellular metabolism in the mitochondria. Cancer cells favor a metabolic shift that prioritizes glycolysis regardless of oxygen availability (36). Typically, when oxygen is available, the end product of glycolysis, pyruvate, would enter into the citric acid cycle (aka Krebs cycle) and proceed with oxidative phosphorylation. In many cancer cells pyruvate is converted instead into lactate. This metabolic transformation leads to dependence on glucose for cancer cell survival and an overexpression of glucose transporters GLUT1 and GLUT3 at the cell membrane. The process allows for the study of tumor progression using PET scans with radiolabeled glucose (15). Many tumor cells lack the ability to effectively utilize ketones because of mitochondrial dysfunction (37). A ketogenic diet lowers the availability of glucose to tumor cells while providing ketone bodies to healthy cells. There is evidence that ketogenic diets will increase oxidative stress in tumor cells, making them more vulnerable to radiation and chemotherapy (38). In addition there is likely an effect of the ketogenic diet on tumor cell-signal molecules such as insulin-like growth factor (IGF)

and mechanistic target of rapamycin (mTOR), which play a role in tumor cell propagation (37). Numerous case studies and reviews show promising benefits of a ketogenic diet in the treatment of various cancers in people (15, 37, 39, 40). However, some cancers have different metabolic demands and may not respond (19). Furthermore, due to challenges inherent in standardizing dietary protocols, until more research is performed it is difficult to make definitive recommendations regarding ketogenic diets as an adjunctive treatment for cancer. To date, there are no studies evaluating ketogenic diets in dogs for this purpose. However, there is a growing interest among pet owners and the veterinary community, spearheaded by a non-profit organization (b) which reports many anecdotal benefits of the diet in dogs.

There is promise that ketogenic diets may improve neurologic function in human patients with amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), multiple sclerosis (MS), and Parkinson's disease because mitochondrial dysfunction is at the root of most neurodegenerative diseases. Neuronal loss and accumulation of amyloid  $\beta$ -peptide and neurofibrillary tangles in the brain are the hallmarks of AD in people. These findings are remarkably similar to the analogous disease in dogs, canine cognitive dysfunction (41). The exact cause is unknown but is likely multifactorial including genetic and

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epigenetic factors. In patients with AD, downregulation of glucose transporters leads to the impaired ability of neuronal mitochondria to take up glucose and complete glycolysis. This results in starvation of the neural tissue, causing inflammation and oxidative stress, ultimately leading to progressive cognitive and motor decline (42). Most previous strategies to combat AD have focused on prevention of the accumulation of amyloid plaques and neurofibrillary tangles. Therapies to date have been largely unsuccessful, and research emphasis has been shifting towards evaluation of energy metabolism in the brain, supporting metabolic therapy as a promising line of treatment. Ketones can provide an alternative energy to glucose-resistant neurons. Furthermore, a ketogenic diet has been shown to have a potent antioxidant effect in the brain (43). A study in rats showed that ketones protected hippocampal neurons from amyloid- $\beta$  toxicity (44). Several studies have shown cognitive improvement in humans with mild or early onset AD with ketogenic strategies (18, 45-47). In addition to AD, amyotrophic lateral sclerosis and multiple sclerosis have also shown improvement with the use of a ketogenic diet (1, 17, 48, 49). In dogs, research on the effects of diet on neurodegenerative disease and cognitive decline is limited. However, some studies have shown improved performance with cognitive tests when dogs were given a diet supplemented with MCTs (50, 51). MCTs can provide an alternative fuel source for the brain when glucose metabolism is impaired, reducing amyloid accumulation and improving mitochondrial function (41).

Due to the exceptionally low carbohydrate content in a ketogenic diet, it makes sense that this dietary strategy would be successful in treating patients with Type II diabetes. Type II diabetes, characterized by high levels of insulin and insulin resistance, results in hyperglycemia. Insulin levels and associated negative metabolic effects are dramatically reduced with a ketogenic diet. Obesity is correlated with diabetes, and a ketogenic diet has been shown to cause weight loss by various mechanisms including increases in satiety, lipolysis, metabolic expenditure of protein metabolism, and insulin sensitivity/glycemic control (14, 52, 53). MCT supplementation has also been shown to reduce insulin resistance and suppress body fat accumulation (54). While there are no studies to date evaluating a ketogenic diet to help manage diabetes in companion animals, the general strategy of lowering carbohydrates has been shown to be beneficial. Several commercial diets (c, d, e) have been formulated with a lower carbohydrate content specifically to help manage this condition.

## Monitoring

Periodic monitoring is needed to ensure that the ketogenic diet is appropriate and that a state of nutritional ketosis

is maintained. Ketones can be measured in a number of ways, but the easiest method is by using a urinary dipstick. Urine strips were developed to help prevent human diabetics from unknowingly entering into a state of diabetic ketoacidosis. Strips only measure acetoacetate and can provide only a subjective estimation of a state of ketosis by analyzing a semi-quantitative color change on the dipstick. Furthermore, as the metabolic machinery shifts to more efficient ketone utilization, urinary ketones will drop even in a state of ketosis. Measurement of BHB in the blood is preferred because of the interpretive errors with urinary dipsticks. Ketones rise in the blood before they are present in urine, and blood measurements provide a more accurate absolute value. Several studies have validated the use of a portable handheld device (f) to measure blood BHB in dogs (55-57). Monitoring blood ketones helps ensure that the pet's diet is formulated correctly and that compliance is being met. Lower readings are expected in dogs compared to those reported in people because of the differences in ketone metabolism between dogs and humans. There is debate over the value of the absolute number, as a higher measurable ketone level is not necessarily better. Until more research is performed, a probable ideal range for nutritional ketosis (based on anecdotal reports) would be a BHB measurement between 0.3 to 1 mmol/L in the dog.

## Potential Challenges

The major hurdle to overcome when initiating a ketogenic diet, especially in animals, is the inconvenience. Commercially available ketogenic diets are sparse; however, a few are available (g, h). A home-prepared diet allows easier fine-tuning of the ingredients and macronutrient ratios. Feeding a ketogenic diet requires very precise macronutrient calculations and is typically extremely limited in ingredients, which makes home preparation easier. If not formulated correctly, micronutrient deficiencies may occur. A state of ketosis will only be reached if dietary carbohydrates are continuously kept below a certain threshold. Even one lapse in the strict diet may prevent ketosis from being achieved. Despite the limited room for error, a ketogenic diet can be appropriately formulated to be nutritionally complete. Obtaining advice from a board-certified veterinary nutritionist or at least someone that is familiar with ketogenic diets is recommended. Adverse effects, while relatively uncommon, may occur when transitioning to a ketogenic diet. Diarrhea or vomiting may occur early in the transition but are generally self-limiting and likely induced by changes in the gut microbiome as the gastrointestinal tract adapts to a very different macronutrient ratio. Some pet owners may fear that the diet is unpalatable to their dog because it is eating less. This is an expected change in behavior as a ketogenic diet is much more

satiating. Because of the higher calorie content of fat (9 kcal/gram) versus protein (4 kcal/gram) or carbohydrate (4 kcal/gram), the actual volume of food eaten will be less because the food is more energy dense. In fact, it is not uncommon for some dogs to completely skip meals. There is often a concern for the possibility of developing pancreatitis because of the high fat content in a ketogenic diet. Pancreatitis is a complex inflammatory disorder with multifactorial causes. Fats and other nutrients that have been cooked at high temperatures have the potential to generate more of an inflammatory response compared to other fresh foods that have not been cooked at high temperatures. The systematic heating and processing of food can cause excessive accumulation of advanced glycation end products (AGEs), which are linked to higher levels of oxidative stress and inflammation (58). In this author's experience the development of pancreatitis is not a major concern when using fresh foods that have not undergone rancidity or oxidation by exposure to high heat. Nonetheless, one must consider prior medical problems and/or medications administered that may increase the tendency to develop pancreatitis (ie, prior episodes of pancreatitis, corticosteroid treatment, etc.). In people, there is a concern with the diuretic effects of a ketogenic state leading to electrolyte loss, particularly of sodium, potassium, and magnesium. These imbalances are often used to explain what is referred to as the keto flu, described as lethargy, weakness, muscle cramps, dizziness, irritability, and gastrointestinal distress. It is generally well accepted that electrolytes play an important role in this phenomenon; however, more research is needed to answer the questions regarding why it occurs and how to prevent it. Anecdotally in both humans and dogs, electrolyte supplementation appears to mitigate these symptoms. As with any dietary intervention, individual variation and modifications should be expected.

## Conclusion

The ketogenic diet involves several mechanisms through which physiology throughout the body can be altered. Currently, it is an untapped strategy for treating and preventing disease in veterinary medicine. With the guidance of a trained professional, the ketogenic diet can be another tool to help manage several chronic diseases. Much more research is needed on the short- and long-term effects of a ketogenic diet in dogs, but there will likely be more discussion in the near future as emerging evidence supports its use.

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## Acknowledgements

The author declares that there are no conflicts of interest.

## Endnotes

- a. Purina® Neurocare™, Nestle Purina Petcare Company, St. Louis, MO
- b. KetoPet Sanctuary, KetoPet, Georgetown, TX, website: <https://www.ketopetsanctuary.com>
- c. Hill's® Prescription Diet® m/d®, Hill's Pet Nutrition, Topeka, KS
- d. Purina® DM Dietetic Management™ Cat Food, Nestle Purina Petcare Company, St. Louis, MO
- e. Royal Canin® Veterinary Diet Glycobalance™, Royal Canin, St. Charles, MO
- f. Precision Xtra Blood Glucose and Ketone Monitoring System, Abbott Laboratories, Abbott Park, IL
- g. Ketonatural Pet Foods™, Salt Lake City, UT, website: <https://ketonaturalpetfoods.com>
- h. Visionary Pet Foods, Los Angeles, CA, website: <https://visionarypet.com>

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