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Reviewing the potential link between grain-free diets and dilated cardiomyopathy in canines

By

Larissa Webster

An undergraduate honors thesis submitted in partial fulfillment of the requirements for the degree of

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Abstract

Grain-free diets for dogs are becoming increasingly popular, but concerns are emerging following the FDA's recent investigation that there might be a link between grain-free diets and DCM in dogs with no known genetic predisposition. Contrary to the majority of the public thought, dogs do nutritionally require grains, and there is rarely a medical reason to switch to a grain-free diet. Not all cases of DCM are linked to diet, and many dogs who are fed grain-free diets do not develop the disease; the extent of this issue therefore is not entirely known. This review aims to explore what is known about DCM and grain-free diets and discuss the issues in researching this potential tie. DCM is linked to grain-free diets mainly through inadequately low taurine levels, due to the grain-free substitutes that have skewed macro nutritional ratios and poor bioavailability.

Owning a dog offers many challenges and, in the modern day, technology allows for such a quantity of pet products to be advertised and available that it can be confounding to pick even a basic product: dogs' food. With the pet market on the rise, businesses employing effective marketing strategies, and the pet food market guidelines scarcely being monitored, it is not surprising that fad and boutique diet types are flying off the shelves with little regard to short– or long–term effects on pets. Among the most popular of these are grain–free diets. However, evidence is emerging that these grain–free diets may not be as healthy as marketed, and in contrast may be causing a fatal disease, Dilated Cardiomyopathy (DCM), in dogs with otherwise no known genetic or environmental predisposition to the disease.

Dog Domestication

Dogs first were domesticated in Eurasia around 10,000 years ago, although the exact date remains open to debate (Skoglund et al. 2011). The magnitude of the domestication or, more particularly, the effects of domestication on dogs, that has taken place since then has induced remarkable morphological and behavioral changes relative to the wild ancestors. These changes in turn led to potentially profound physiological modifications. While wolves and dogs are classified as the same species, *Canis lupus*, their DNA, although differing only by less than 1%, is divergent in regions that lead to significant contrasts in lifestyle and that have induced physiological peculiarities in each lineage (Linblad-Toh et al. 2005).

Domestication has changed the way dogs receive food: wolves typically are feeders on large, sporadically available prey. Thus, they can consume large quantities at one time, then withstand long periods of fasting. In contrast, while dogs are able to fast, they have consistently and, more importantly, regularly been fed for the past $\gtrsim$11,000 years. As a result, they are fairly reliant on humans to provide food. It currently is hypothesized that early in domestication, humans likely provided dogs with grain surpluses and scraps during the agricultural revolution; this diet eventually led to changes in dogs' nutritional requirements (Axelsson et al. 2013). Wolves taxonomically are classified as members of the order Carnivora, or carnivores; while they do occasionally consume plant matter, it is thought to act as more of a scouring agent to clear intestinal parasites than for nutritional benefit; the overall vegetal matter consumed is negligible in wolves' diet (Bosch et al., 2015). Dogs also taxonomically are carnivores, but ecologically belong to the trophic guild of omnivores: they require supplementation from a meat diet. This difference between wolves and dogs clearly is evident in the distinction between wolves' and dogs' macronutrient requirements (Bosch et al. 2015).

A recent study by Axelsson et al. (2013) showed that dogs had several genes coding for starch digestion that were not present in wolves: dogs had thirty to forty copies of the amylase gene, a protein that begins the breakdown of starch in the mouth and the small intestine (duodenum, via the pancreatic duct), whereas wolves only have two copies. The net result is that the gene in dogs is potentially 28–fold more active than in wolves. Axelsson et al. (2013) also found that dogs' copy of *MGAM*, the gene coding for maltase (another enzyme important in starch digestion, one that spatially co-occurs in the body with amylase), is longer in dogs, making it more typical of herbivorous and omnivorous organisms, and also making their maltase more efficient than that of wolves. These results support the idea that dogs require grains in their diet, and that their nutrient needs differ from those of their ancestors. This would disprove the Ancestral Diet Theory: the argument that dogs need similar nutrients and diets as wolves. If dogs do from an evolutionary perspective nutritionally require grains, it begs the question: why are dogs being fed grain-free diets?

Grain-Free Diet Myths

The surge of gluten and grain-free products in the human food market has caused a similar wave of thought regarding the pet food market. Many pet owners assume that grain-free pet products are more natural, carbohydrate-free, and cause fewer health problems, such as allergies. However, as outlined above, dogs do needs grains and carbohydrates, and grain-free foods oftentimes will have different macronutrient levels: while they are lower in carbohydrates, they have higher levels of fat and calories, which can lead to many other serious health issues, including weight gain, diabetes, and cirrhosis of the liver, when fed long-term to dogs (Kaiyala et al. 2000; Chaikoff and Conner 1940). There is a misconception that whole grains act as fillers, offering little-to-no nutritional value; however, whole grains provide vital nutrients such as vitamins, minerals, essential fatty acids, and also provide protein that even may be easier to digest than meat-based proteins (Burns 2018). Some grain-free diets are substituted with highly refined starches like potatoes, that have less nutrients and fiber, and are not as cost-efficient as normal grains. Some diets use beans, peas, and lentils (sometimes called pulses), which can potentially lead to further gastrointestinal upset. Other substitutes such as sweet potato have higher carbohydrate levels than the most common grain in pet foods, which likewise could throw off the macronutritional ratios (Burns 2018).

The most common misconception about grain-free diets is that they are better for dogs with food allergies and insensitivities, as it often is in humans. Many food allergies in dogs manifest as dermatitis, causing itchy skin and hotspots, but in fact, less than one percent of skin diseases in pet dogs are caused by grains, and grains cause less than 10 percent of all allergies. Grain allergies are much more uncommon in pets: problems almost always are caused by the protein source. The most common food allergies in dogs are beef, chicken, and dairy, and in cats are dairy, fish, and chicken (Burns 2018). Proteins are often the culprit due to their large and complex structure; if the amino acids are not fully broken down, the enterocytes in the small intestine may not absorb the protein and mark it as foreign, triggering an immune response (Olivry et al 2017). Allergies can develop to anything, but these food allergies are most common likely because they are also allergies to the most common ingredients in pet food. Gluten intolerances are even more uncommon and only are known to exist in only one family of inbred Irish Setters and is essentially non-existent in cats (Daminet 1996). Overall, there is little-to-no scientific reason why grain-free diets would be the diet of choice unless the animal has been diagnosed with a rare grain allergy.

Dilated Cardiomyopathy

Dilated cardiomyopathy (DCM) is a heart disease that causes the heart to weaken and enlarge; it affects both right and left sides of the heart, usually enlarging both ventricles and atria while thinning the surrounding muscular walls (PennVet 2013). In some breeds of dogs, the disease appears to affect one side of the heart more than the other. Both manifestations of DCM impair the heart's ability to pump blood to the body: if the ventricles are affected, the ability to pump blood throughout the body is

impaired. If the left side of the heart fails, then fluid can collect in the lungs, and if the right side fails, fluid can collect in the abdomen or chest cavities, both of which are likely fatal (2013). Onset of thedisease can be sudden or progressive.

Diagnosis of this disease can be difficult because while heart abnormalities can be identified upon exam, a definitive diagnosis involves an echocardiogram and possibly radiographs to assess the presence of fluid build-up (CornellVet 2018). The criteria of Kaplan et. al (2018) for a DCM echocardiographic diagnosis was that two of four principles had to be met: left ventricular percent fractional shortening (% FS) < 25%, percent fractional area change (% FAC) < 35%, percent ejection fraction (% EF) < 40%, and left ventricular internal diameter at end-systole (LVIDs) > 3.5cm. Difficult diagnosis only further complicates the matter of treatment and research involving this disease.

Long-term prognosis of DCM is unpromising but variable. Symptoms may progress slowly but almost all cases lead to heart failure - when the heart fails to pump adequate blood to the body. Dogs diagnosed with DCM that are not yet in congestive heart failure may do well with clinical treatment for 1-2 years, while most dogs already in congestive heart failure unfortunately die within 6 months (PennVet 2013). Treatment aims to improve heart function and control the onset of congestive heart failure with a variety of medications such as pimobendan to help the heart contract, diuretics to control fluid accumulation in and around the lungs, ACE inhibitors like enalapril to open the arteries and assist with pumping, and more.

There is a known genetic predisposition in certain dog breeds, usually large or giant breeds such as Doberman pinscher, Newfoundland, Portuguese Water dog, Boxer, Great Dane, Cocker Spaniel, and Irish Wolfhounds. However, studies have found that the genetic basis varies (Broschk 2005). An autosomal dominant inheritance is seen in Newfoundlands and Boxers, while an autosomal recessive inheritance was found in Portuguese Water Dogs, and an X-linked recessive inheritance is likely in Great Danes. There seems to be a predisposition bias by sex as well, affecting male dogs more often than female dogs (Broschk 2005). In humans, there are several known gene mutations responsible for DCM predisposition, but not much else is known about the underlying cause of the canine predisposition besides the few gene mutations and modes of inheritance found.

Emerging Concerns

In July 2018, the FDA announced an investigation into a potential link between grain-free diets and canine DCM due to numerous reports of dogs developing DCM in breeds without genetic predispositions; many of these dogs had been fed grain-diets (FDA 2018). Many of the diets reported to the FDA frequently list potatoes or multiple legumes such as peas and lentils as their main ingredients. There has been an update following the first announcement in June 2019, providing further detail on the reports, listing the most frequently affected breeds, ages, weights, and sexes of individuals reported, and naming the most frequently named dog food brands and their ingredients (FDA 2019).

This second statement reports a total of 515 canine cases of DCM [in dogs with no known predisposition] between 1 January, 2014 and 30 April, 2019; 222 of these occurred between 1 December, 2018 and 30 April, 2019. There were 9 cases in felines, but this article focuses on canines, as feline DCM is less common than hypertrophic cardiomyopathy, and a landmark paper showed that DCM in cats is associated with a taurine deficiency, which has since been classified as an essential amino acid for felines (Pion et al., 1987). The FDA report names the three top dog breeds most frequently reported as: golden retrievers, mixed, and Labrador retrievers, with the average age of 6.6 years, average weight of 67.8 lbs, and a 58.7:41.3 ratio males to females (FDA 2019). It should be noted that Labrador retrievers are the most common breed in the United States and golden retrievers are third most popular, so the results may be skewed towards certain breeds only because they appear most frequently in the population (American Kennel Club 2018). Almost all reported cases were fed dry-type foods, and the three most frequently reported brands were Acana, Zignature, and Taste of the

Wild. However, many other brands also were listed with great frequency. There was no single animal protein source used: the most common were chicken, lamb, and fish.

The FDA report touches on a few possible causes of this surge of DCM cases. It was mentioned that since the July 2018 report, the FDA and Vet-LIRN have tested products labeled "grain-free" for protein, fat, moisture content, crude fiber, total dietary fiber, soluble and insoluble fiber, total starch and resistant starch, and cysteine, methionine, and taurine levels. These all had similar results compared to grain-containing products (FDA 2019). Because DCM is known to be caused by low taurine levels in cats, researchers focus on low taurine levels and DCM in dogs. Unlike in cats, taurine is not considered an essential amino acid for dogs because they have to ability to synthesize taurine from cysteine and methionine. Taurine therefore is not added into most dog foods, so the methionine-cysteine concentration is the important measure when considering taurine availability in dog food. Nearly all the grain-free products tested were above the minimum nutritional requirement of 0.65% methionine-cystine, but it is possible that taurine absorption and excretion may have a role in DCM regardless of the presence of taurine's precursors.

Taurine

Taurine is a sulfur-containing amino acid and is one of the most abundant free amino acids in the body that—unlike most other amino acids—is not incorporated into proteins (Sanderson, 2006). It is found in high concentrations in cardiac muscle, skeletal muscle, the central nervous system, and platelets (Tenaglia and Cody 1988). The function of taurine is not well understood in mammals but is highly diverse. It now is generally concluded that taurine deficiency can cause DCM and is widely associated with the disease (see studies below).

Taurine is considered an essential amino acid in cats and its absence is known to cause DCM in this species as well as retinal degeneration and reproductive anomalies (Pion et al. 1987). Taurine is not considered an essential amino acid in dogs in part because they have higher levels of the rate-limiting enzyme cysteine sulfinic acid decarboxylase, which is essential in the synthesis of taurine from cysteine and methionine (Jacobsen et al., 1964) and can therefore be naturally synthesized from a normal diet. However, there may be more to the story than just the presence of the enzyme: this enzyme is found in even lower levels in healthy adult humans than in cats, although taurine is not an essential amino acid in humans.

Research undertaken to address the concerns between grain-free diets and DCM have largely focused on taurine deficiencies. While its role is not exactly clear, it is known that taurine plays an essential role in cardiac function and that deficiencies in taurine can have many side-effects including DCM. Because it was proven that taurine deficiency was the cause of many cats developing DCM and retinal degeneration in the 1980's, a similar line of thinking—that taurine deficiencies could cause DCM in dogs—was considered and supported by evidence in the studies outlined below.

Taurine deficiencies are difficult to identify in dogs because the dogs themselves can have taurine deficiencies even when fed a diet with sufficient taurine levels. There also is debate as to what test is the best to accurately measure body taurine levels. Most studies use plasma or whole blood taurine concentrations; however, results may differ between whole blood, plasma, urine, or fecal, taurine levels, or between fecal bile acids. The current theory is that the ingredients commonly used in grain-free diets as substitutions, such as legumes and potatoes, are interfering with the normal metabolism of taurine or its building blocks, causing the patients to become deficient, and thereby potentially causing DCM. So, it is not just the absence of grain that is the problem in grain-free diets, it is more of a multi-factorial issue involving the body's ability to synthesize taurine from the unusual ingredients in these foods.

Taurine Studies

Researchers from the University of California, Davis conducted a study that showed when fed taurine-free diets or diets found to be taurine-depleting in cats, a group of eight healthy beagles did not result in becoming taurine depleted (Pion et al. 1992). This study showed that taurine could not become depleted in dogs from diet alone, and in combination with an additional study conducted at this university, showed that taurine did not play a considerable role in the development of DCM in dogs. This study was challenged when DCM was shown to be linked to a taurine deficiency in foxes in 1989 (Moise 1989). A new study was subsequently initiated in collaboration between UC Davis and the Animal Medical Center in New York City that evaluated plasma taurine levels in dogs with DCM and dogs with chronic degenerative mitral valve disease, another common cardiac disease in dogs. Results showed that 17% of 76 dogs with DCM had low plasma taurine levels (< 25 nmol/mL), and seven of the thirteen dogs with low taurine levels were in breeds not commonly afflicted with DCM, such as American cocker spaniels and golden retrievers (Kramer 1995). However, it was concluded that taurine deficiency was unlikely to play an important role in DCM because the plasma taurine concentrations in breeds that are more commonly afflicted with DCM were within reference range.

All three American cocker spaniels (ACS) in the previous study tested with low taurine levels, which spurred on the Multicenter Spaniel Trial (MUST). This study started by taking baseline plasma taurine concentrations and echocardiograms of all 11 ACSs diagnosed with DCM; all dogs had low taurine concentrations (< 50 nmol/mL; note that this is a different level than that of the Kramer study; Kittleson et al. 1997). The dogs were then randomly assigned supplementation of taurine and *L*-carnitine (a derivative of lysine and methionine important for myocardial function) or a placebo for 4 months. Dogs receiving supplementation showed significant echocardiographic improvement while the placebo dogs did not. After the 4-month period, the dogs receiving the placebo also were given supplementation, likewise resulting in echocardiographic improvement. The improvement was not as dramatic as taurine supplementation in cats diagnosed with DCM but was significant enough to discontinue cardiovascular drug therapy. The mean survival time was 28.3 ± 19.1 months, a great improvement from the average 6-month survival with conventional therapy. The study concluded that taurine and carnitine supplementation should be the recommendation for American cocker spaniels diagnosed with DCM.

Another study was conducted at the University of Minnesota around the same time as the MUST study (S. L. Sanderson, unpublished data 1998). This study examined dogs who developed DCM after long-term consumption of a protein-restricted diet that was being used to manage urolithiasis. The breeds included English bulldogs, Dalmatians, and a miniature Dachshund. The study split the dogs into two groups: Group 1 received conventional drug therapy alone, while Group 2 received both conventional therapy and taurine and/or carnitine supplementations. Two of the most important findings of this study were that three of the eight dogs in Group 2 were cured of DCM, and that, contrary of previous thought, dogs fed a protein-restricted diet long-term can develop a taurine deficiency.

To further evaluate the effects of long-term taurine deficiency on cardiac function in healthy dogs, particularly in light of the study outlined above, an additional experiment was undertaken involving 17 healthy adult beagles (Sanderson et al. 2001). Once baseline plasma and whole blood taurine levels, and echocardiography data were collected, dogs were fed one of three protein-restricted diets for 48 months: all three diets had similar levels of protein and all had methionine and cysteine levels at or above the recommended levels by the Association of American Feed Control Officials (AAFCO). However, one also was low in fat, a second was high in fat, and a third was high in fat and supplemented with *L*-carnitine at 200 mg/kg of diet. Plasma and whole blood taurine levels, and echocardiography, were evaluated every 6 months. All three diets caused a significant decrease in whole blood taurine concentrations, and the high-fat group also experienced a significant decrease in plasma taurine levels. One dog with taurine deficiency developed DCM, and taurine supplementation resulted in an almost complete reversal of the disease. This study was the first to show that diet could induce taurine deficiency in healthy adult dogs, that taurine

deficiency preceded DCM, and that taurine supplementation substantially improved cardiac function. The mechanism of why dogs developed taurine deficiencies while consuming a protein-restricted diet is unknown, but this study showed that the AAFCO recommended minimum requirements for amino acids may need to be modified in certain types of diets.

Lamb and Rice Diets and Alternative Hypotheses

Other examples of diet-induced taurine deficiencies in dogs include a study carried out on dogs fed a tofu-based diet, which concluded that the taurine deficiency was attributed to the protein source being soybean curd, which is low in sulfur-containing amino acids and completely devoid of taurine compared to meat-based proteins (Backus et al. 2003). Lamb meal and rice diets were explored in the same study, which found that the taurine deficiency in 12 Newfoundlands consuming two different lamb and rice diets were reversed when the diet either was changed or supplemented with methionine. Also tested were 12 large and giant-breed dogs consuming commercial diets containing lamb meal, rice, or both, as the primary ingredient, and that had tested positive for DCM and taurine deficiencies, supplementing them with taurine (Fascetti el al. 2003). All dogs showed significant echocardiographic improvement; the authors therefore hypothesized that taurine deficiencies caused DCM and was caused by inadequate or unavailable dietary sulfur–based amino acids that are precursors to taurine. Another report by Bélanger et al. (2005) showed that three of five golden retrievers tested were fed lamb meal and rice or lamb and rice diets, and all showed significant improvement after taurine supplementation, allowing all dogs to live more than 3 more years. The authors suspected DCM to be caused by an autosomal recessive mode of inheritance, but there is potential in the role that diet played in the taurine deficiency.

Another study done at UC Davis by Tôrres et al. (2003) compared two groups of 12 healthy beagles who were fed either a lamb and rice-based, or poultry by-product-based diets. Results showed no differences in plasma and whole blood taurine concentrations between diet groups, but the taurine levels excreted in urine were less in the lamb and rice-fed dogs. Taurine homeostasis in dogs primarily is by the regulation of renal taurine excretion, so urinary taurine excretion is an accurate indicator of taurine absorption/synthesis. The authors had similar conclusions to those of Fascetti et al. (2003): support for the hypothesis that reduced bioavailability of sulfur amino acids in the lamb and rice diets are the cause of the taurine deficiency.

A second hypothesis has been supported in particular by Delaney et al. (2003) and Stratton-Phelps et al. (2002), who hypothesized that low quality dietary proteins, possibly lamb, serve as a substrate for bacterial growth in the colon when parts thereof are undigested. Some bacteria produce cholyltaurine hydrolase, an enzyme that releases taurine from bile acids, which results in increased taurine fecal output/loss. Rice bran and whole rice provides fermentable fibers that may increase bacteria in the colon and could subsequently lead to taurine loss in fecal matter, as well as affecting taurine metabolism through altering intestinal bacteria from the high fat content associated with rice products.

A more recent study (Pezzali et al., 2020) based their experiment on the above hypothesis, comparing the effects of grain-based and grain-free diets on protein utilization and taurine status in healthy adult beagles. Two diets were formulated with the same ingredients with the exception of the carbohydrate sources: grain-based food contained sorghum, millet, and spelt, while the grain-free contained potatoes, peas, and tapioca starch. They found that overall whole blood, plasma, and urinary taurine status was not affected by dietary treatments, but that the fecal primary bile acid excretion (measured instead of fecal taurine concentrations, because intestinal bacteria can degrade in the colon) was higher in grain-based diets, indicating that the higher oligosaccharides and soluble fibers in the grain-free diets may alter the composition of fecal bile acids. The authors suggested that microbiota should be considered an essential factor in fecal bile acid profile in dogs, and therefore in taurine concentrations.

Taurine and Grain-Free Diets

Summarizing the studies discussed above, the current thoughts are 1) that taurine and carnitine supplementation is beneficial in dogs with DCM and is likely to cause improvement (sometimes a complete reversal, sometimes just lengthening survival time); and 2) that taurine deficiencies could originate from particular diet-types such as low-protein and high-fat. Different protein sources such as lamb may contain varying levels of sulfur-containing amino acids that affects taurine synthesis in dogs, potentially causing a deficiency. Bacteria in the colon also may play their part in the development of taurine deficiencies based on protein types and fat content; similarly, carbohydrate sources also may alter taurine levels in the body.

While some studies found that taurine deficiencies could precede DCM, and that supplementation could potentially reverse the disease, there also are many cases of non-genetically predisposed dogs with DCM that do not have taurine deficiencies, making it difficult to conclude with finality if DCM and taurine have a cause-and-effect relationship. The FDA investigation reported that all products labeled as grain-free had similar levels of percent protein, fat, total taurine, total cystine, total methionine, total methionine-cystine, and resistant starch content, on a dry matter basis, to grain-based products. This can rule out the simple hypothesis that grain-free diets simply are low in sulfur-containing amino acids, thus causing a taurine deficiency leading to DCM (FDA 2019). It is also reported that "nearly all" (it is not specified which) of the grain-free products tested above the minimum nutritional requirement of 0.65% for adult dog foods set in place by AAFO. However, as discussed above, the AAFCO requirements may not be sufficient in all cases. No one animal protein source dominated the grain-free products tested, so it also is difficult to conclude that the digestibility or quality of varying proteins would greatly affect taurine levels. The carbohydrate sources did vary, with a greater number of peas and/or lentils containing-products than potatoes or sweet potatoes, which may be altering colon microbiota and fecal taurine output.

Are grain-free diets causing DCM?

Unfortunately, this is not a simple conclusion and further research needs to be carried out to determine the relationship between grain-free and dilated cardiomyopathy. The answer is multi-faceted but likely revolves around taurine and its bioavailability in the body, which can be influenced by macronutritional ratios, such as low-protein or high-fat foods, and the effect of various ingredients such as legumes, which may have more significance in grain-free foods than grain-containing foods on the microbiota of the colon, and which could lead to taurine loss. Taurine and *L*-carnitine supplementation is the current recommendation for DCM cases and is likely to improve the outcome of the disease. Veterinarians remain undecided on diet recommendations, as dietary-induced DCM associated with grain-free diets remains unproven, but the established links are suggestive, and the diet should be considered as a potential underlying cause or contributing to dogs presenting with DCM.

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