# Grain-free diets and dilated cardiomyopathy – our understanding to date

Nick Cave
BVSc MVSc PhD MANZCVS DipACVN
Associate Professor in Small Animal Medicine and Nutrition
School of Veterinary Science
Massey University

In New Zealand, where we remain blissfully free of heartworm, dilated cardiomyopathy (DCM) is probably the second most common cardiac disease affecting dogs, after myxomatous valvular degeneration. DCM should strictly be defined as a primary myocardial disorder characterized by reduced contractility, and ventricular dilation involving the left or both ventricles, and is idiopathic or genetic in cause.[1] Most cardiologists insist that when a cause other than genetics is known, the disease is not called DCM, but rather as "cardiomyopathy" of that cause. The example *du jour*, is "taurine deficiency cardiomyopathy", though that has not been widely accepted. For simplicity, and in keeping with the literature on the subject at the moment, I will adopt the plebeian approach, and refer to taurine as a cause of DCM.

## Taurine and DCM

Taurine is an amino acid that is not incorporated into proteins, but has a very high intracellular concentration, notably in neurons, myocytes, and some leucocytes, and has the highest intracellular-to-plasma concentration gradient of all the normal amino acids. The functions of taurine are many, but osmoregulation and calcium regulation are perhaps the two most important. As an osmoregulator, it is very important in neurons, which accumulate high concentrations during sustained dehydration to preserve cellular integrity without disturbing the membrane potential. In muscle, taurine facilitates the binding of $Ca^{2+}$ to actin, although when asked to explain what that means, the cognoscenti usually engage in a lot of hand waving, and resort to terms such as "not completely elucidated". Nonetheless, in deficient states, there is a reduction in actively contracting elements, and a reduction of the shortening fraction of the ventricle. The reduced cardiac output results in activation of the renin-angiotensin system, and initiation of remodelling pathways to cause eccentric hypertrophy. The resulting increase in wall stress exacerbates the contractile failure, leading to more remodelling, and subsequently, clinical DCM.

Taurine deficiency was identified as a cause of DCM in cats in 1987.[2] Not long after, the same phenomenon was identified in the US in farmed foxes that were fed diets that contained only a small amount of taurine.[3] At that time, it was apparent that domestic dogs differed from foxes, because it had been shown that dogs can synthesise taurine from the dietary sulphur amino acids, methionine and cysteine. However, cats have a very high rate of amino acid oxidation, and have lost any appreciable synthetic capacity, meaning they have a dietary requirement. Similarly, foxes probably have a very low synthetic capacity, meaning that they may have an absolute dietary requirement. And other than cats, dogs, and foxes, taurine deficiency can cause DCM in humans, rats, and giant anteaters. And probably many other species.

Dogs and cats differ from mice and men in, amongst other things, the bile salts they synthesise. Bile salts are synthesised from metabolites of cholesterol, of which there are many, but the most common are cholic acid, and chenodeoxycholic acid. To make these functional bile salts, they are conjugated to a water soluble compound. Humans and rodents conjugate most bile acids to glycine, and a small amount to taurine. In contrast, dogs and cats both exclusively use taurine as the conjugate, and cannot switch to glycine conjugation in taurine deficiency.

Once secreted into the intestine, a proportion of bile salts are hydrolysed by the bacterial enzyme bile salt hydrolase (BSH), yielding a bile acid, and its free conjugate. The conjugate

is then available for fermentation by bacteria and is lost to the host. To date, more than 100 different genera of bacterial species are known to express BSH, although the amount expressed by the whole intestinal bacteriome varies massively between individuals.[4] Thus, different individuals can have very different taurine turnover, or in the case of dogs and cats, requirements, simply because of the bacteria present in their intestines.

Initial studies into taurine requirements in cats revealed that a cat requires more dietary taurine if it is being fed a canned diet, than when being fed a kibbled diet.[5] The difference can be completely abolished if the cats consuming the canned diet are treated with oral antibiotics, which highlights the role of the intestinal bacteria in causing taurine depletion.[6] The difference in diets was related to the creation of maillard compounds (browning products) during the heating process.[6] These compounds decrease the digestibility of the protein, and provide substrate that promots the proliferation of BSH-expressing bacteria. Surprisingly, at least to me, was that we did not detect a significant expression of that, or similar enzymes in the faecal bacteriome of cats fed canned or dry diets in our colony.[7] That remains an inconvenient and mysterious side note for the time being. Nonetheless, modification of the intestinal bacteriome can lead to increased loss of intestinal taurine, and over time, depletion of body stores, and clinical deficiency.

As noted above, dogs are capable of synthesising taurine, and it is not considered an essential nutrient. However, in the early part of the century, dogs with DCM and taurine deficiency were being seen.[8] The mechanism in those cases turned out to be identical to that defined in cats. Certain diets modified the bacteriome and led to bile salt degradation and depletion of taurine. If those diets had a low content of methionine and cysteine, and no taurine, then the dogs were unable to synthesise enough, and deficiency developed. Features that were common to the diets originally incriminated were: no added taurine, low protein content, low methionine/cysteine content, low protein digestibility, and the presence of rice bran. A cruel twist of fate occurred when Nutro, who produced of one of the incriminated diets, sponsored and provided food for the Newfoundland breeders association in the US.[9] A perfect storm. Rice bran appeared to be particularly potent at bacterial modification, and was shown to be capable of accelerating taurine deficiency in cats fed an supplemented diet.[10] Manufacturers had several options to dietary correction: increase the protein content, add supplemental methionine/cysteine, change the fibre content, or simply add taurine. Problem solved. Or at least, that is what was thought.

**Grain-free diets and DCM**

In July 2018, the US Food and Drug Administration (FDA) announced it was investigating a possible link between cases of canine DCM and certain diets.[11] At time of writing, they have produced data on 515 cases reported to the FDA from January 1st 2014, to April 30th 2019 (Figure 1). They have released the list of brands “incriminated”, but it would be very hard to conclude a causal relationship, since there is uncertainty of the temporal association, most dogs were exposed to multiple foods, and there is a growing potential for recall bias amongst owners and veterinarians. Nonetheless, more than 90% of products were marketed under the moniker “grain-free”, and 93% of reported products included peas and/or lentils as significant ingredients.

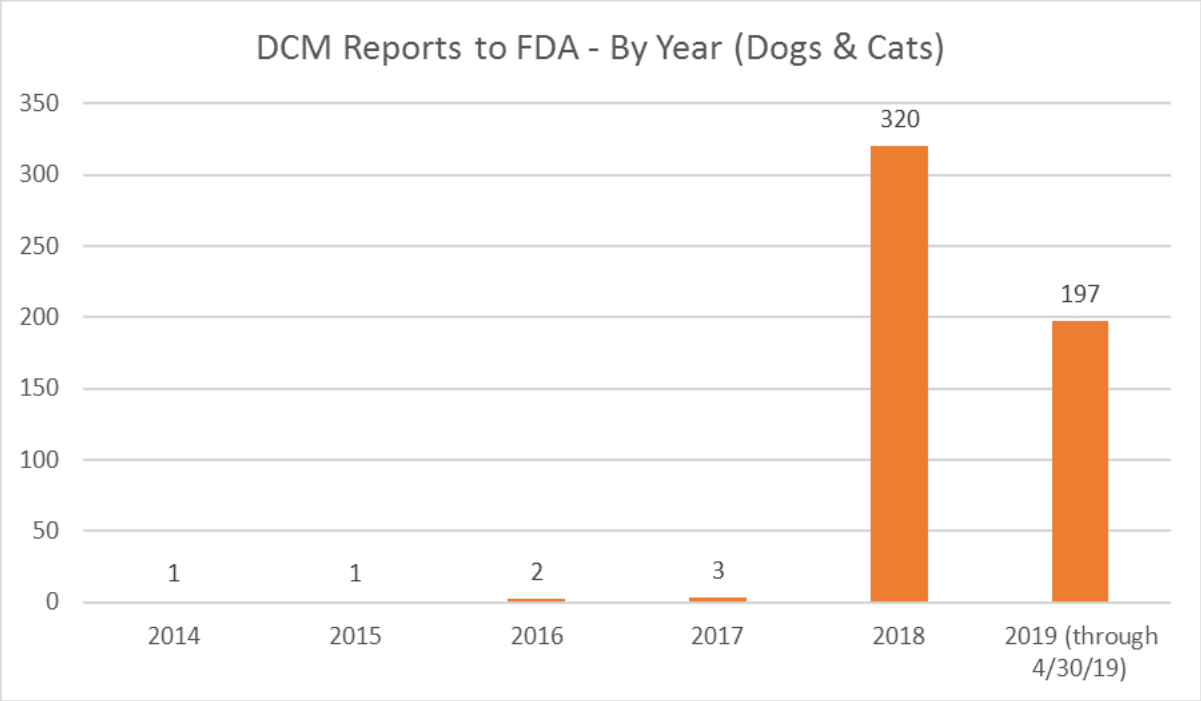


Figure 1. Reports of DCM made to the US Food and Drug Administration. Between January 1, 2014 and April 30, 2019, the FDA received 524 reports of DCM (515 canine reports, 9 feline reports).[11]

Of the diets most strongly associated, there are some familiar common themes. Small or new manufactures are prominent. A complete absence of testing via feeding trials. The use of unconventional ingredients with unknown digestibilties. The use of protein sources with low contents of sulphur amino acids (legumes). And probably all are rich in plant fibres that have similar or identical effects to the rice bran. And of course none have adequate taurine to offset those features.

The list of breeds, is almost completely concordant with the relative risk of DCM in those breeds coupled with the breed popularity (Figure 2). In fact, of the breeds identified, only Shi Tzu and Pitbulls are not reported breeds of predisposition that I am aware of - if you count arrhythmogenic right ventricular cardiomyopathy as a cause of DCM (Table 1). And even for those two outlier breeds, severe mitral valular disease can lead eventually to myocardial failure that can be difficult to distinguish from primary DCM. Given that the cases were not necessarily diagnosed by a cardiologist with exclusion of other causes, we cannot be confident. Yet had the list been dominated by atypical breeds, it would have been greater cause for concern as to a novel mechanism. Nonetheless, of those cases specifically investigated, taurine deficiency is prominent. In a case series of 24 Labrador Retrievers investigated between 2016 and 2018 at UC Davis (not all included in the FDA series), 23 were taurine deficient.[12] Several different diets had been fed, but none of the diets had been tested using Association of American Feed Control Officials (AAFCO) procedures.

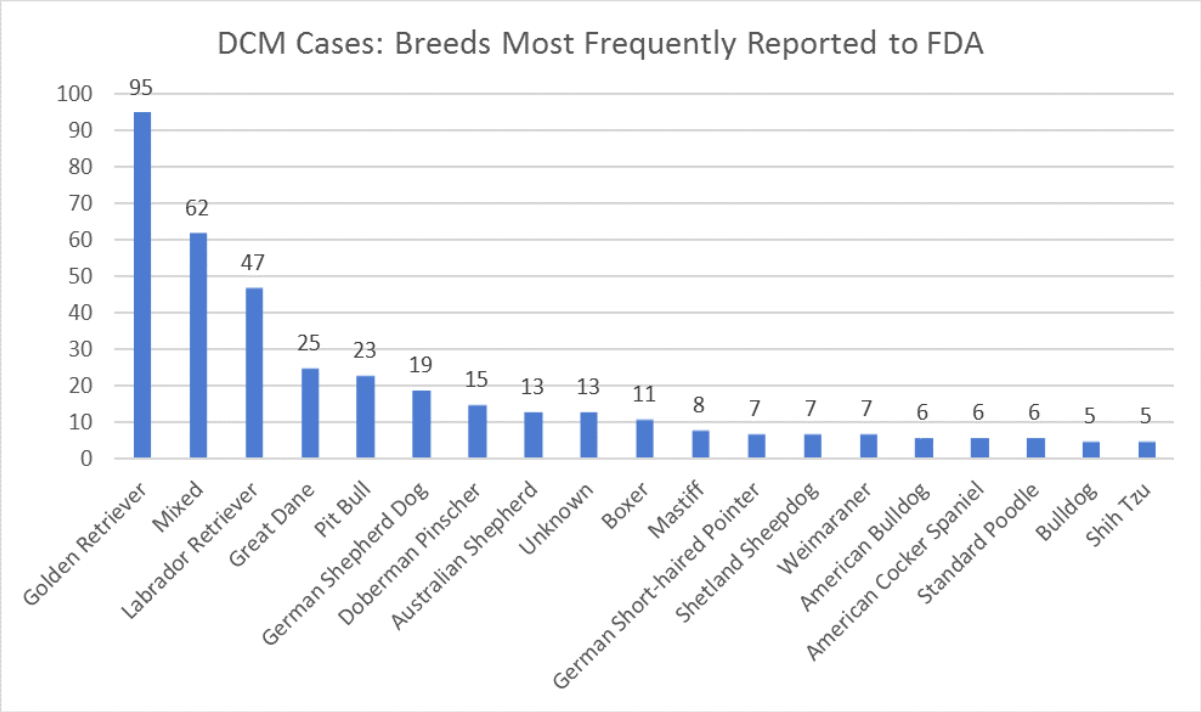

Figure 2. Breeds of dogs with DCM most commonly reported to the FDA.[11]

With the exception of the study by Kaplan et al (2018), the quality of information available at present is low.[12] The FDA data set does not have any case controls, and only a subset were tested for taurine deficiency. In addition, the almost complete concordance between affected breeds and breeds of predisposition, and the inconsistency of diagnosis, means that many of the cases were almost certainly breed-associated DCM that were not caused by any dietary effect. Perhaps the most pressing need is to determine if there are cases of DCM in atypical breeds that are not taurine deficient. To emphasise the point, only 1 of the 5 Shi Tzu's in the FDA case series was tested for taurine deficiency, and it was not deficient. However, it had an antibiotic-responsive cough, and there was no information on an echocardiographic diagnosis beyond "heart enlargement on radiographs".

Since 2010, there has been a startling increase in the number and sales of "grain-free" pet foods globally. Their popularity in the US forced even conventional heavyweights such as Hill's Pet Care to hop on the bandwagon ("Ideal Balance Grain Free" range). Sales of "grain-free" diets increased in the US from US$900 million, to US$3 billion between 2011 and 2016, and was the market segment responsible for growth during that period.[13] In short, if you are a new manufacturer, you will want to enter the market with a "grain-free" product.

New and small pet food manufacturers very rarely test products with feeding trials, few have veterinary nutritionists even consulting for them, and many have no animal nutritionist at all. Quality control, consistency of ingredients, careful monitoring of animals fed their diets, and a clear understanding of the problems, are frequently lacking in small and new companies. In contrast, better manufacturers use established ingredients, perform appropriate testing, prove dietary adequacy through feeding trials, have excellent quality control procedures, batch test their products, and have a deep understanding of the complexities that actually lie behind the deceptively simple appearing task of manufacturing dog food.

**Conclusion and recommendations**

So what should our approach to this subject be? Clearly the "absence of grains" is irrelevant to whether a diet is good or bad, though that hasn't stopped many commentators from suggesting that dogs "should be fed diets that contain grains". Since dogs don't have a requirement for "grain", the absence of "grain" cannot be causal, after all, the diets are also free of rhino horn, tuatara, and the penises of capybara, and they aren't suggested as causes. In addition, diets that are free of grains have been fed for eons in various forms, notably in this country, where the basic ingredients are not as readily available. Lastly, several excellent companies manufacture diets marketed as "grain free" that clearly do not cause DCM.

So, perhaps I can suggest a few precepts to help the daily grind, and fend off the difficult conversations:

1. Only encourage owners to feed diets that have been formulated to meet the requirements established by AAFCO or FEDIAF.
2. If asked for a specific recommendation, I think we should recommend diets that have been proven in AAFCO / FEDIAF feeding trials.
3. Make sure you understand the added value that manufacturers give when they produce diets using high quality ingredients that they understand, have rigorous quality control regimes, test diets appropriately both in the laboratory and in the animal, and truly know what they are doing. We are not hiding behind corporate muscle like scared sycophants in so doing, we are standing behind our recommendations because of the confidence in the products. I want to have confidence that the diets I feed my animals are complete, balanced, and appropriately tested.
4. Recognise that "grains" are no more responsible for adverse food reactions than any other major conventional ingredients, and whilst they are neither essentially good nor bad, they can be a source of highly digestible and essential nutrients, and there is no nutritional value to avoiding them in the diet of dogs.
5. The success of "grain free" diets is a triumph of marketing over evidence, and the label is neither a mark of quality, nor deficiency. I would happily feed a diet from Hill's Ideal Balance Grain Free range, not because it is grain free, but because it is good. I would *unhappily* feed my dog a diet from a small manufacturer that has not demonstrated they have formulated the diet properly, has not tested the diet in a feeding trial, and about which I know nothing, irrespective of whether it is grain free or not.
6. At this point in time, a dog presenting with DCM that is on a diet about which you are not confident, should be treated with taurine until you have reason not to, and the owner offered the option of a taurine assay. Taurine is cheap, readily available, non-toxic, and taurine deficiency cardiomyopathy is reversible.
7. Dog breeds of predisposition for DCM eating "grain free" diets, can develop DCM independent of the diet.
8. If you have a suspicion of any adverse reaction to any diet, please report it to the wonderful people of the ACVM (ACVM-adverseevents@mpi.govt.nz).
9. If you wish to directly quiz a manufacturer, consider asking the following:
    - How do they ensure their diets are complete and balanced?
    - Have they tested whole blood taurine in dogs fed their diets for long periods?
    - What is the taurine content of the diets?
    - What is the protein and sulphur amino acid content?
    - What is the protein digestibility?
10. It remains to be seen if there is any mechanism other than taurine deficiency by which the current diets are causing DCM in dogs.

**Taurine supplementation**

Give 500 mg per 10kg, up to a maximum of 2000mg orally per day. It does not have to be given twice daily, and can be given with, or without food.

**Taurine assay**
Taurine can be assayed by the Massey University Nutrition Laboratory. Whole blood taurine is a better indicator of long term status than plasma taurine, and only slightly affected by recent intake. The assay involves lysis of the blood cells to release taurine into the plasma. Plasma taurine gives a shorter term status, but is more susceptible to error from leakage of taurine from cells. Serum taurine is an unreliable measure because of wide variations in leakage from cells, and cannot be interpreted.

Collect at 2 ml of venous blood into heparin, and freeze promptly. Although heparinised whole blood can be couriered unfrozen if shipped on the same day as collection, it is not recommended as the Massey University Nutrition Laboratory does not offer a clinical diagnostic service, and delays in sample handling can be significant.

Send frozen samples with cold packs to:
Felicity Jackson
IFNHH Reception
Nutrition Laboratory
Riddet Building
Massey University
Palmerston North
New Zealand

Please recognise that this is not a clinical diagnostic service, so it is recommended you contact the laboratory prior to submission to check pricing, turnaround times, etc.

Table 1. Breeds in which dilated cardiomyopathy has been reported.[14-20]

| Breeds |
|---|
| Afghan Hound |
| Airedale Terriers |
| American Cocker Spaniel |
| Australian shepherd |
| Bearded Collies |
| Belgian shepherd |
| Bloodhounds |
| Border collie |
| Border terrier |
| Bouvier des Flandres |
| Boxer |
| Bull Mastiffs |
| Cavalier King Charles spaniels |
| Cocker spaniel |
| Crossbreed (!) |
| Dalmatian |
| Deerhound |
| Doberman Pinscher |

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| Dogue de Bordeaux |
| English bull terrier |
| English Cocker Spaniel |
| English Sheepdog |
| Flat-coated retriever |
| German shepherd dog |
| German shorthaired pointer |
| Golden retriever |
| Gordon setter |
| Great Dane |
| Irish Setters |
| Irish wolfhound |
| Labrador Retriever |
| Leonberger |
| Neapolitan mastiff |
| Newfoundland |
| Old English sheepdog |
| Pyrenean mountain dog |
| Red setter |
| Rottweiler |
| Saint Bernard |
| Salukis |
| Scottish Deerhound |
| Siberian Huskies |
| Springer Spaniel |
| Staffordshire bull terrier |
| Standard Poodles |
| Standard schnauzer |
| Weimaraner |

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