

GRAIN FREE DIET & CARDIOMYOPATHY

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Commentary

Diet-associated dilated cardiomyopathy in dogs: what do we know?

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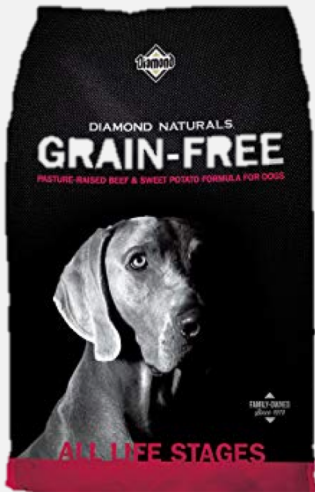
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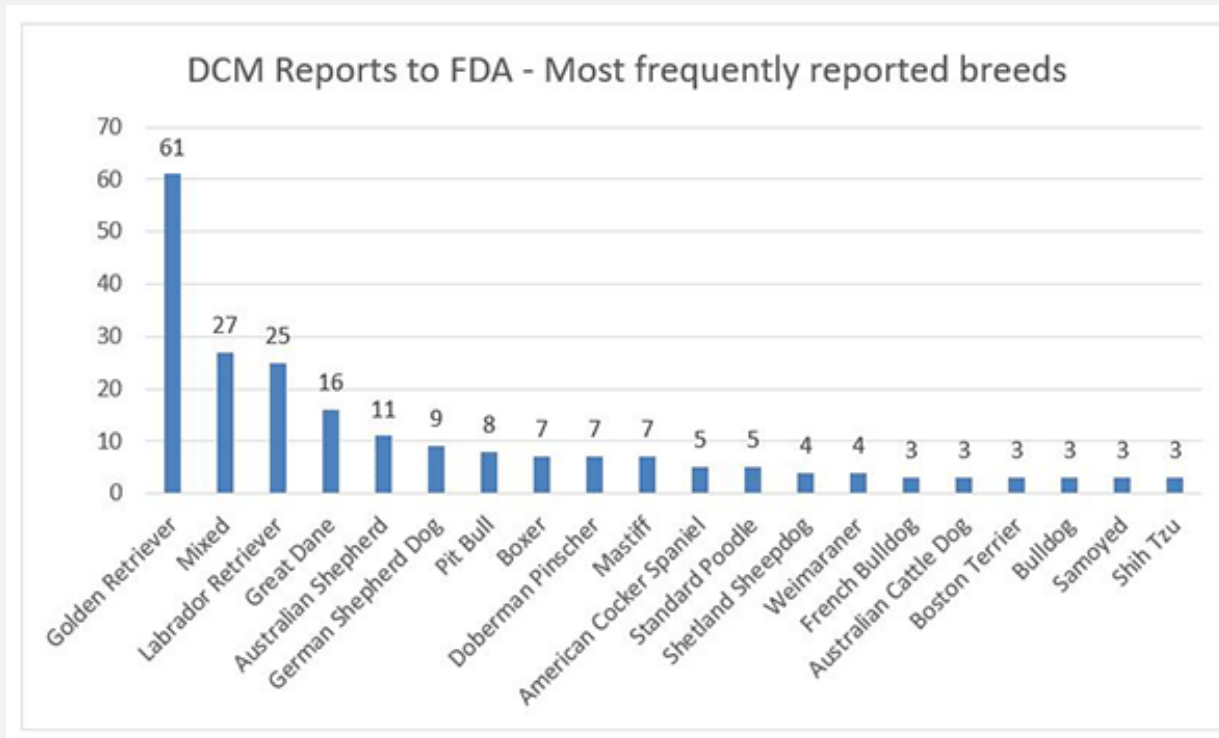
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WHY THE CRAZE?



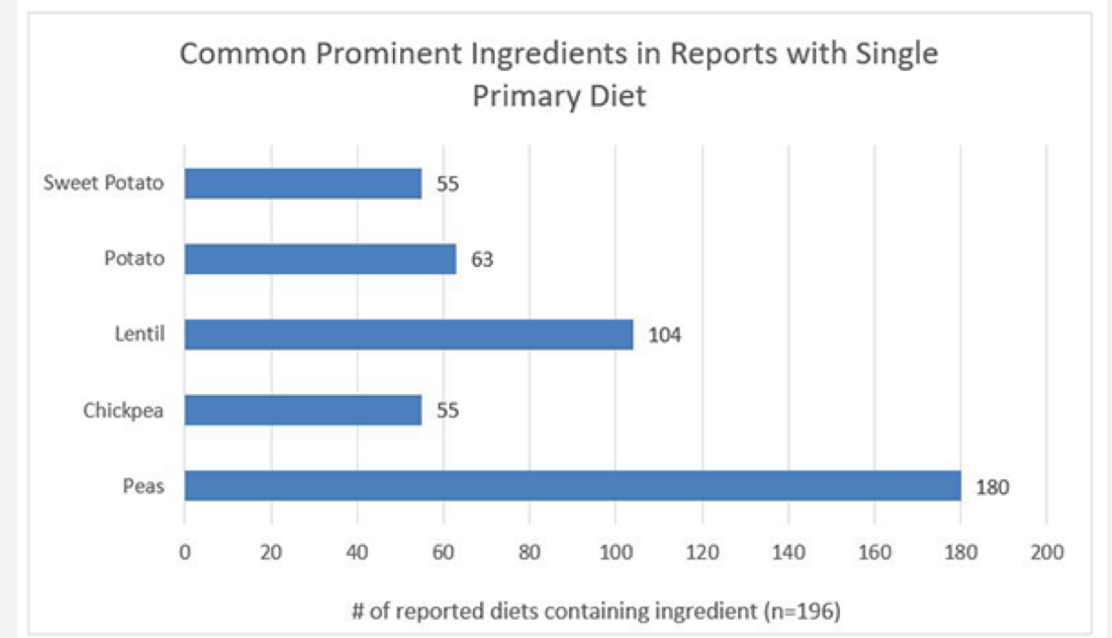
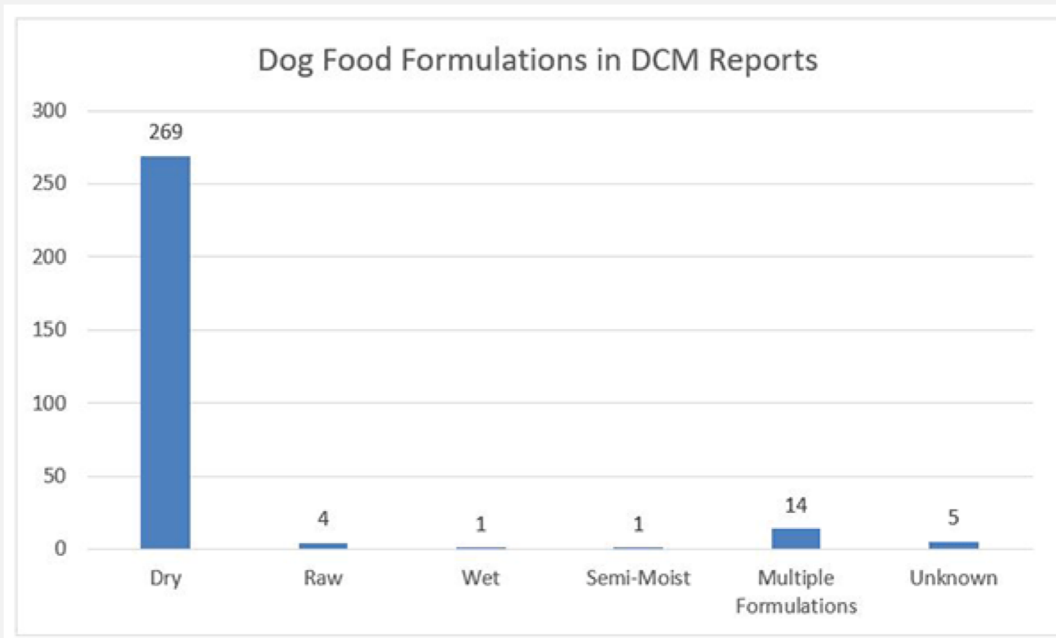
- There is an increased of feeding unbalanced home-prepared diets, raw diets, vegetarian diets, and boutique, exotic-ingredient, and grain-free (BEG) diets
- In July 2018, FDA announced its investigation into relationship between canine DCM and certain pet foods containing high proportions of peas, lentils, and other legume seeds (pulses) and/or potatoes
- DCM was being reported in breeds that were not previously known to have a genetic predisposition to the disease
- DCM was being reported in dogs eating a BEG diets both with or without taurine deficiency

FDA STATISTICS



- Between 01/04/2014 - 11/30/2018, FDA received 294 reports of canine DCM

FDA STATISTICS



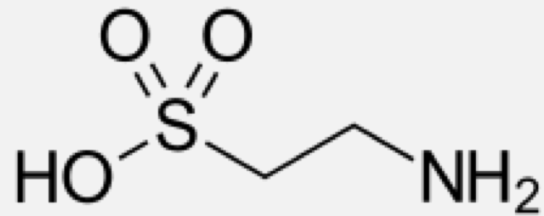
- 90% of dogs who were fed a single primary diet were given a “grain-free”/BEG diet
- Large proportion of reported diets in DCM cases contained peas and/or lentils

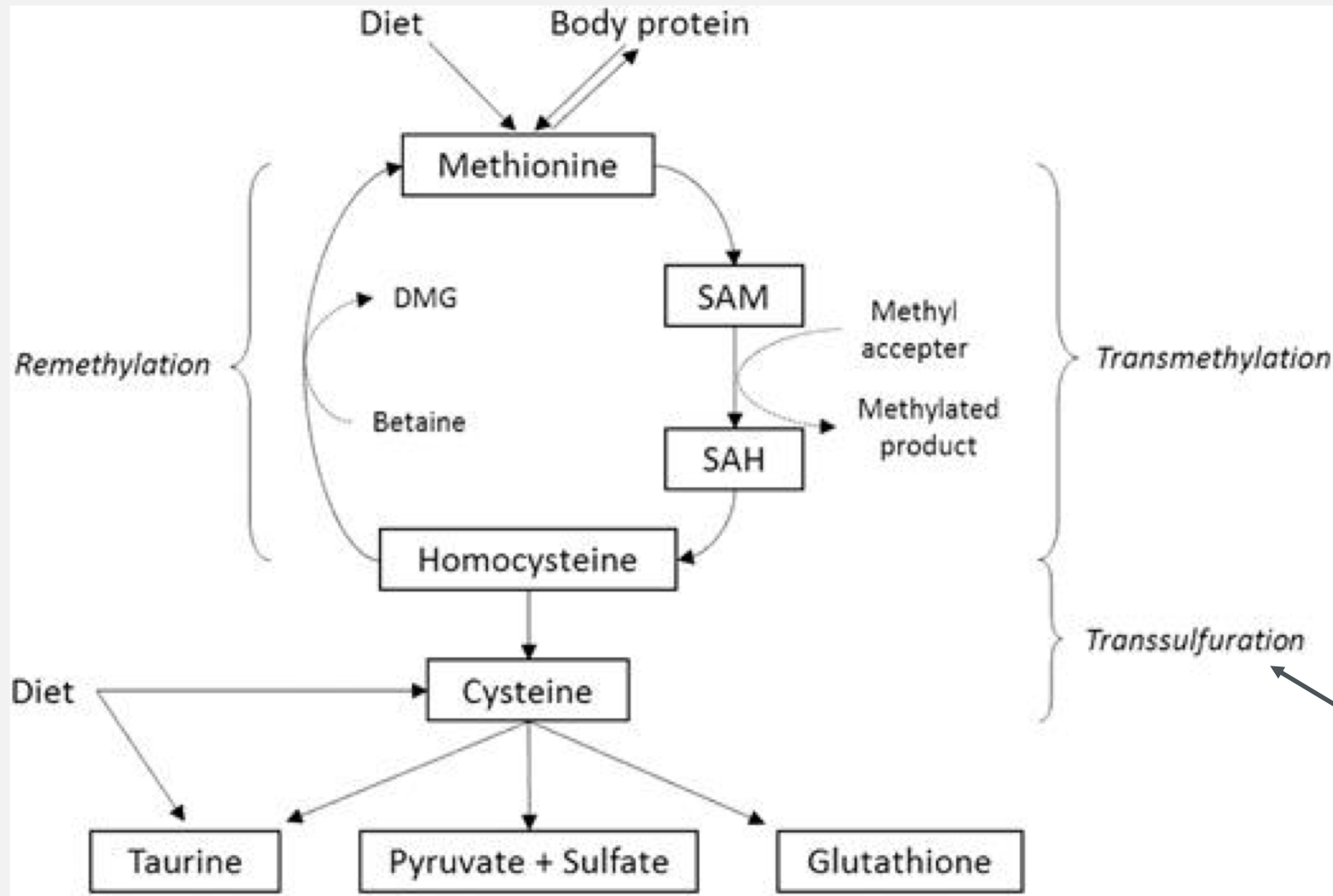
DILATED CARDIOMYOPATHY (DCM)

- Disease of the myocardium that results in both mechanical dysfunction (enlarged heart cavities and congestion) and/or electrical dysfunction (arrhythmias and sudden death)
- Genetic predisposition in several large and giant breeds
 - Dobermans, Boxers, Great Danes, Irish Wolfhounds
- Golden Retrievers and American Cocker Spaniels predisposed to taurine deficiency
 - Other at increased risk breeds: Newfoundlands, St. Bernards, English Setters, Irish Wolfhounds, and Portuguese Water Dogs.

TAURINE

- Sulphur-containing amino acid (AA)
- Primarily synthesized from methionine and cysteine in the liver and CNS
 - Non-essential AA in dogs
- Taurine ~60% of the total AA free pool in the heart

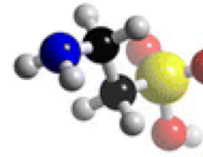




Cats have low enzyme activity here -> limits endogenous synthesis

TAURINE

- Taurine contributes to the reabsorption of calcium by the sarcoplasmic reticulum and increases the sensitivity of the myofilaments to calcium
- Any many more...

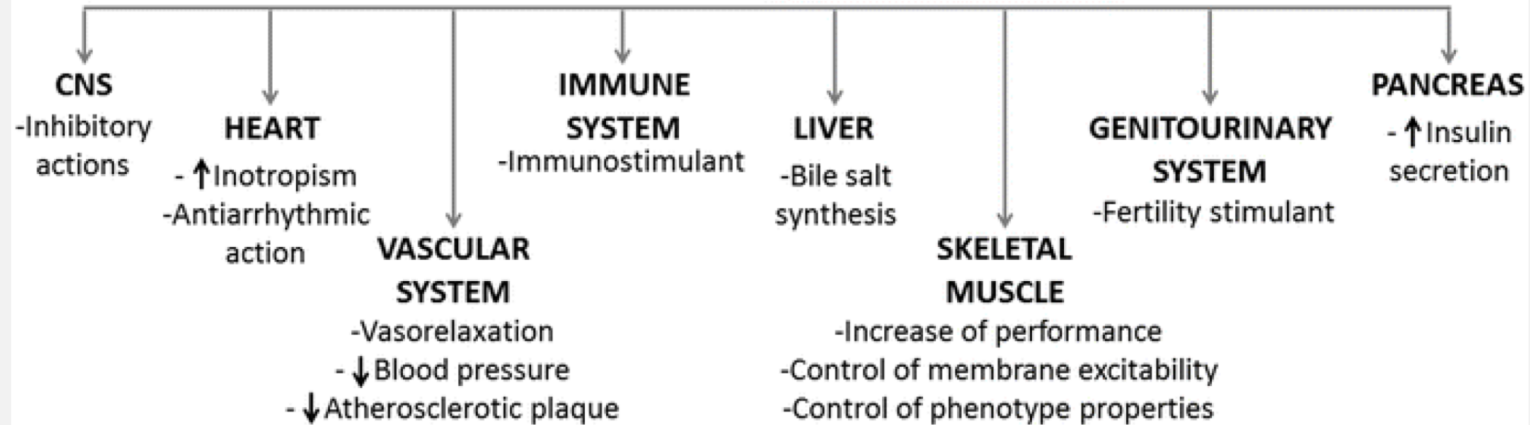


Taurine

General Actions

- Osmolyte
- Ion channels regulator
- Intracellular calcium regulator
- Antioxidant
- Anti-inflammatory
- Anti-proliferative
- Anti-endoplasmic reticulum stress

Main target tissues



TAURINE

- Nearly all of the grain-free products had methionine-cystine values above the minimum nutritional requirement for adult maintenance food for dogs published in the AAFCO Official Publication (OP).
- Low dietary taurine intake and/or reduced synthesis of taurine from methionine and cysteine → deplete Ca^{2+} pool in cardiac cells
 - → Impede proper contraction of the cardiac muscle tissue → DCM

Special topic: The association between pulse ingredients and canine dilated cardiomyopathy: addressing the knowledge gaps before establishing causation¹

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ABSTRACT: In July 2018, the Food and Drug Administration warned about a possible relationship between dilated cardiomyopathy (DCM) in dogs and the consumption of dog food formulated with potatoes and pulse ingredients. This issue may impede utilization of pulse ingredients in dog food or consideration of alternative proteins. Pulse ingredients have been used in the pet food industry for over 2 decades and represent a valuable source of protein to compliment animal-based ingredients. Moreover, individual ingredients used in commercial foods do not represent the final nutrient concentration of the complete diet. Thus, nutritionists formulating dog food must balance complementary ingredients to fulfill the animal's nutrient needs in the final diet. There are multiple factors that should be considered, including differences in nutrient digestibility and overall bioavailability, the fermentability and quantity of fiber, and interactions among food constituents that can increase the risk of DCM development.

Taurine is a dispensable amino acid that has been linked to DCM in dogs. As such, adequate supply of taurine and/or precursors for taurine synthesis plays an important role in preventing DCM. However, requirements of amino acids in dogs are not well investigated and are presented in total dietary content basis which does not account for bioavailability or digestibility. Similarly, any nutrient (e.g., soluble and fermentable fiber) or physiological condition (e.g., size of the dog, sex, and age) that increases the requirement for taurine will also augment the possibility for DCM development. Dog food formulators should have a deep knowledge of processing methodologies and nutrient interactions beyond meeting the Association of American Feed Control Officials nutrient profiles and should not carelessly follow unsubstantiated market trends. Vegetable ingredients, including pulses, are nutritious and can be used in combination with complementary ingredients to meet the nutritional needs of the dog.

TAKE AWAY POINTS

- Pulse ingredients have been used for many years
 - Represent a valuable source of protein to compliment animal-based ingredients.
- Multiple factors should be considered that may increase risk of DCM
 - Differences in nutrient digestibility
 - Overall bioavailability
 - Fermentability and quantity of fiber
 - Interactions among food constituents
 - Individual dog characteristics

TAKE AWAY POINTS

- The relationship between pulses and canine DCM remains undefined
- Endogenous and exogenous taurine may be both important
 - Need to take into account appropriate concentrations of all indispensable sulfur AAs, including methionine and cysteine,
- Further empirical data and mechanistic studies are required to better understand the indispensable AA requirements of dogs and preventing DCM

Taurine deficiency and dilated cardiomyopathy in golden retrievers fed commercial diets

Introduction

Golden retrievers are over-represented in cases of taurine-deficient dilated cardiomyopathy and recently a surge in cases has prompted further investigation.

Objective

To describe the clinical, dietary, and echocardiographic features in golden retrievers diagnosed with taurine deficiency and dilated cardiomyopathy, and to determine specific dietary associations. A second aim was to determine the whole blood taurine concentrations in a representative sample of healthy golden retrievers.

Animals

Twenty-four client-owned golden retrievers with documented taurine deficiency and dilated cardiomyopathy and 52 healthy client-owned golden retrievers.

Methods

In this multicenter prospective observational study, baseline and follow-up echocardiographic data, complete diet and medical histories, and whole blood, plasma, or serum taurine concentrations were obtained. Baseline and follow-up echocardiographic data were compared. Associations were evaluated between specific diets and taurine deficiency or congestive heart failure. The prevalence of low whole blood taurine concentrations in the healthy golden retrievers was calculated.

Results

Twenty-three of 24 dogs diagnosed with taurine deficiency and dilated cardiomyopathy were fed diets that were either grain-free, legume-rich, or a combination of these factors. None of these diets were feeding trial tested using Association of American Feed Control Officials (AAFCO) procedures. Twenty-three of 24 dogs had significant improvement in their echocardiographic parameters and normalization of taurine concentrations following diet change and taurine supplementation. Nine of 11 dogs diagnosed with congestive heart failure (CHF) had resolution of their congestion at follow-up with five no longer requiring diuretic therapy and four tolerating diuretic dose reduction by >50%.

Conclusions

Certain diets and diet characteristics were associated with the development of taurine deficiency. Taurine deficiency and dilated cardiomyopathy in golden retrievers is likely multifactorial, including a combination of dietary, metabolic, and genetic factors.

TAURINE-DCM IN GOLDEN RETRIEVERS

- Largest prospective, multi-center observational study to date evaluating DCM in Goldens
- 24 with documented taurine deficiency + DCM and 52 healthy controls
- "Affected" dogs recruited in North America either PP or University between Jan 2016-July 2018
- Data collected: signalment, history, PE, routine echo, WB/plasma/serum taurine levels, RER/energy requirements
- Follow up needed for repeat taurine levels, diet histories, echos
- Prescribed Taurine at median dose 3000 mg PO q8-12h



TAURINE-DCM IN GOLDEN RETRIEVERS

- DCM diagnosis: FS <25%, FAC <35%, EF <40%, LVIDs >3.5cm
- LA enlargement defined as La:Ao ratio ≥ 1.6
- LV enlargement defined as LVIDd > 5.1
- Taurine deficiency defined as WB < 250nmol/mL, plasma < 60nmol/mL, or serum < 110nmol/L
- Diets
 - All ingredients recorded and assessed
 - Caloric content, crude fibre, moisture, total dietary fibre, insoluble fibre, and soluble fibre recorded
 - Diets considered to have legumes (peas, lentils, beans, chickpeas) as primary ingredient if included in first 5 listed ingredients

Table 2. List of pet food brands with their diet varieties and characteristics. For each pet food variety, the number of dogs diagnosed with DCM fed this diet and the number of dogs with taurine deficiency fed this diet were listed. Diet 1a is the same dog receiving diet 9m. The one dog receiving diet 1a is the same dog receiving diet 9m. Note that one dog receiving diet 1a is the same dog receiving diet 9m. Note that one dog receiving diet 1a is the same dog receiving diet 9m.

Diet Brand	Diet Variety	No. of dogs with DCM	No. of dogs with Taurine Deficiency	Meets AAFCO Guidelines	Meets WSAVA Guidelines	G	L
1	a	10	10	✓	No	✓	✓
	b	4	4	✓	No	✓	✓
	c	1	1	✓	No	✓	
2	d	1	1	✓	No	✓	✓
3	e	1	1	✓	No	✓	✓
	f	1	1	✓	No	✓	✓
4	g	1	1	✓	No	✓	✓
5	h	2	2	✓	No	✓	✓
6	i	1	1	✓	No	✓	✓
7	j	1	1	✓	No	✓	✓
8	k	1	1	✓	No	✓	✓
	l	1	1	✓	No	✓	✓
9	m	1	1	✓	No	✓	



- 10/23 dogs with DCM had diet 1a (ACANA Singles Limited Ingredient Diet Pork & Squash Formula)
 - Statistically significant ($p = 0.0012$) association between diet 1 and taurine-concentration
- None of the diets underwent feeding trials for nutritional adequacy
- None of these diets met WSAVA guideline
- Total dietary fiber, insoluble fiber, and soluble fiber concentrations were not available for any diets

RESULTS: HEALTHY DOGS

- In the 52 healthy controls, 43 had complete diet histories
- 12/52 dogs had WB taurine levels 200-250 nmol/mL
 - 10 from this group were on legume-rich +/- GF diets
- 4/52 had WB taurine levels <200 nmol/mL
 - All of them were on legume-rich +/- GF diets
- The diets that were fed to these 14 dogs did not feed WSAVA recommendations
- 27/52 dogs had WB taurine levels >250 nmol/mL
 - 40% of them fed diet met WSAVA recommendations

RESULTS: “AFFECTED” DOGS

- 23/24 diagnosed with taurine-deficient DCM
 - One dog remained in CHF – lack of owner compliance in medication, supplementation and in diet change
- 11/24 were diagnosed with CHF
 - 9/11 of dogs that were in CHF had resolution of congestion
 - 5/11 were weaned off diuretics, 4 weaned by 50%
 - 2 lost of follow-up,
- Other medications (in addition to taurine +/- furosemide)
 - Pimobendan, enalapril, benazepril, spironolactone, diltiazem

RESULTS

- All of the DCM dogs were fed either grain-free, legume-rich, or a combination of these diets
- All of them had significant improvement in their disease after taurine levels normalized
- Many dogs were consuming less than their predicted MER and also less than manufacturer's feeding directions
 - Suboptimal intake → decreased taurine synthetic rates?

DISCUSSION

- Taurine-deficient DCM likely multifactorial
 - May be species variation making them more prone to developing taurine deficiency if taurine not effectively absorbed
 - Exotic meats: certain meats are low in taurine (rabbit) and low in sulfur AA precursors (lamb meal)
 - Bioavailability of taurine & precursors are unknown
- Most dogs were underfed → may have suboptimal intake of sulfur AA precursor

LEGUMES AND TAURINE?

- In certain diets, plants may provide adequate precursors for taurine synthesis.
- However, legumes are limiting in sulfur amino acids
- Legumes contain proteolytic inhibitors and phytates that have anti-nutritional ability → impacts the digestibility and bioavailability of taurine precursor
- Legume is also high in fibre → fibre may result in depletion of taurine in dogs and cats

LIMITATIONS

- Medical therapy, taurine analysis, baseline and treatment period diets, and supplementation were not standardized
- Some were treated with taurine alone, others taurine + L-carnitine
- Taurine testing
 - Lab not standardized
 - Handling not standardized – may cause falsely high (plasma) or low (WB)
 - Not known how accurately WB or plasma taurine levels reflects concentrations in cardiac tissue.
- Did not assess the true prevalence of taurine deficiency in the client-owned golden retriever population

Echocardiographic phenotype of canine dilated cardiomyopathy differs based on diet type[☆]

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Received 30 May 2018; received in revised form 24 October 2018; accepted 6 November 2018



Abstract *Introduction:* Canine dilated cardiomyopathy (DCM) can result from numerous etiologies including genetic mutations, infections, toxins, and nutritional imbalances. This study sought to characterize differences in echocardiographic findings between dogs with DCM fed grain-free (GF) diets and grain-based (GB) diets.

Animals: Forty-eight dogs with DCM and known diet history.

Methods: This was a retrospective analysis of dogs with DCM from January 1, 2015 to May 1, 2018 with a known diet history. Dogs were grouped by diet (GF and GB), and the GF group was further divided into dogs eating the most common grain-free diet (GF-1) and other grain-free diets (GF-o). Demographics, diet history, echocardiographic parameters, taurine concentrations, and vertebral heart scale were compared between GB, all GF, GF-1, and GF-o groups at diagnosis and recheck.

Results: Dogs eating GF-1 weighed less than GB and GF-o dogs, but age and sex were not different between groups. Left ventricular size in diastole and systole

was greater, and sphericity index was less for GF-1 compared with GB dogs. Diastolic left ventricular size was greater for all GF compared with that of GB dogs. Fractional shortening, left atrial size, and vertebral heart scale were not different between groups. Taurine deficiency was not identified in GF dogs, and presence of congestive heart failure was not different between groups. Seven dogs that were reevaluated after diet change (6 received taurine supplementation) had clinical and echocardiographic improvement.

Conclusions: Dietary-associated DCM occurs with some GF diets and can improve with nutritional management, including diet change. The role of taurine supplementation, even without deficiency, is uncertain.

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STUDY DESIGN

- To characterize the differences in echocardiographic findings between dogs with DCM fed grain-free (GF) or grain-based (GB) diets
- Retrospective analysis performed @ NC State
- Enrolled dogs between January 2015 – May 2018

STUDY DESIGN

- Inclusion criteria:
 - Dogs diagnosed with DCM
 - If food brand and variety were known
 - Echo findings: FS \leq 25%, normalized LV internal diastolic diameter (LVIDdN) \geq 1.8
normalized LV internal systolic diameter (LVIDsN) \geq 1.2
- Exclusion criteria:
 - Congenital heart dz, primary valve dz
 - Unknown diet hx, or vegan/vegetarian diets, home-cooked diets

STUDY DESIGN

- Dogs were grouped by diet type
 - Grain-based (GB)
 - Wheat, rice, oats, cornmeal, barley, bulgar, millet, rye or spelt listed as ingredients
 - Grain-free (GF)-I = most common GF diets
 - GF-0 = other GF diets
- Testing
 - Echo
 - Bloodwork: WB or plasma taurine, plasma L-carnitine, selenium
 - Infectious dz testing: Bartonella IFA + PCR, Rickettsia IFA + PCR, Anaplasma IFA + PCR, Babesia PCR, Ehrlichia IFA + PCR, Mycoplasma PCR, Lyme IFA, Trypanosoma cruzi PCR, Leishmania IFA
 - Necropsies when available

RESULTS

- 91 dogs enrolled → 12/48 on GB, 36/48 on GF
 - 43 excluded in group comparison b/c of lack of diet history
- No difference in breed, age, sex b/w groups
- No difference in CHF at time of diagnosis or radiographic heart size
- No difference in FS b/w groups
- GF-I dogs had higher LVIDdN and LVIDsN than GB dogs
- No taurine or L-carnitine deficiencies identified among GF dogs
- Taurine deficiencies detected in 2 dogs fed GB
- 3 GF dogs with post-mortem: no specific etiology of DCM identified

RESULTS

- 7 GF dogs had follow-up echos in 3 months, 2 had follow up in 9 months
 - 6 of these dogs eating GF-1, 1 was eating GF-0
- Diet changed from GF to GB in 5/7 dogs and to "major" GF brand in 2/7
- Taurine supplemented in 6/7 dogs despite normal taurine levels
 - 1/7 dogs showed progressive improvement at 3 and 9 months
 - Same dog's echo normalized 2 years after initially diagnosis of DCM induced CHF
- 1 dog that was not supplemented showed improvement at 9 months that was not seen at 3 months

DISCUSSION

- Improvement in GF dogs after diet change only supports potential causality
- Differences in echo changes suggest a pathologic remodeling process occurring in dogs eating GF diet, esp. GF-I
 - Presumed “diet-related DCM”
- Possible that processing/sourcing of legumes resulted in deficiency or toxicity of important nutrients in a manner that didn’t occur with GB diets
- Unsure if taurine supplementation in face of normal/elevated baseline taurine levels have any effect
 - May be due to taurine’s anti-oxidant, Ca handling effects or +ve inotropic effects

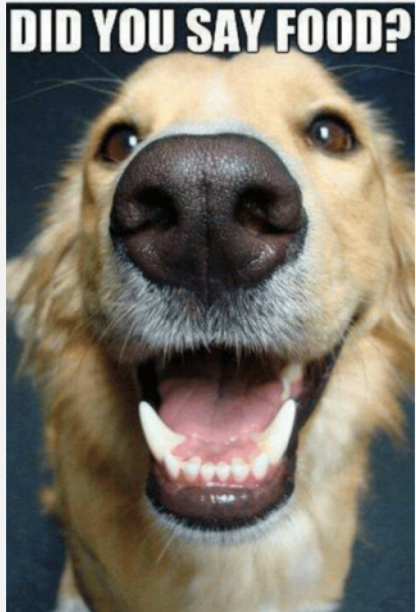
LIMITATIONS

- Retrospective study
- Inconsistent diet history
 - Types of food (including treats), caloric intake, lifestyle
 - Length of time fed a certain diet
- Not all dogs were tested for taurine levels
- Grouping of GF vs GB may be incorrect
 - May be related to underlying “exotic” protein source instead of legumes

IN SUMMARY

- For DCM, we have 3 subgroups of patients
 1. Primary DCM in predisposed breeds, unrelated to diet
 - E.g. Dobermans, Boxers, Great Danes, Wolfhounds
 2. Diet-associated DCM with normal taurine levels
 - Do not know why
 3. Diet-associated DCM with taurine deficiency
 - In breeds predisposed to DCM and breeds that are not predisposed to DCM

WHAT SHOULD WE RECOMMEND?



- DCM in a dog eating BEG diet → measure plasma and whole blood taurine levels
 - Whole blood >> plasma if \$ concern; may be better indicator for long-term status
- In possible diet-associated DCM → switch diet to a well-established manufacturer containing standard ingredients
 - NOT home-cooked or raw diet!
- In possible taurine-deficient DCM → start taurine supplementation pending results
 - 250 mg PO q12h <10kg; 500mg PO q12h 10-25kg; 1000mg PO q12h >25kg
 - Follow up Echo at 3, 6 and 12 months to assess improvement
 - Screen other dogs in the same household eating the same diet
- Grain-free diet NOT recommended unless documented medical condition requiring alteration in dietary ingredients