University of Veterinary Medicine Budapest

Department of Internal Medicine

Diet-related cardiomyopathy in dogs

Literature review and case description

Ann-Marie Wulff

Supervisor: Dr. Gergely Kiss, department engineer

Department of Internal Medicine

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Abstract

Over the last 20 years at least, various case reports and animal studies have suggested a connection between taurine deficiency and the development of dilated cardiomyopathy. Cardiomyopathy is a disease of the heart muscle which can be influenced by dietary factors, such as taurine deficiency. Taurine is a sulphur-containing amino acid which plays an important role in function of the heart, like the regulation of calcium homeostasis, the membrane stabilization, and the antioxidative defence. Despite the growing evidence of the importance of taurine in cardiovascular health, the exact mechanisms which link taurine deficiency to cardiomyopathy remain poorly understood as well as the origin of taurine depletion. This review considers current literature on diet-related cardiomyopathy, which focuses on taurine deficiency as contributing cause for dilated cardiomyopathy. It also examines dietary sources of taurine, metabolic pathways, and its physiological roles in the heart. Lastly it includes cases from the last 2 years, documented at the University of Veterinary Medicine in Budapest, where taurine deficiency was linked to cardiomyopathy in dogs eating hypoallergenic diets. The review also highlights gaps in understanding the causes of taurine depletion and its direct impact on cardiac structure and function with the need for further research to explain the mechanisms behind taurine-deficiency-induced cardiomyopathy.

Content

Introduction

Since 2018 recent reports from the U.S. Food and Drug Administration (FDA) have raised concerns about a potential link between certain pet foods and the development of dilated cardiomyopathy (DCM) in dogs (1). DCM is a condition that weakens the heart muscle, typically seen in large and giant breeds like Great Danes, Boxers, Newfoundlands and Doberman Pinschers, as it often has a genetic origin (2). Interestingly breeds were reported to the FDA which were not genetically predisposed to DCM, including Golden Retrievers, Labrador Retrievers, Whippets, and smaller breeds such as Bulldogs and Miniature Schnauzers, but all consumed a special diet (1). This raises concern that there might be a more complex reason behind the emergence of DCM than simple genetics. Out of common supplements, taurine has a key role in the emergence and therapy of cardiomyopathy. Whereas it is involved in many functions of the body the actual role of taurine in the heart muscle is still not fully understood but suspected to influence the calcium concentration (3). Besides its antioxidant activity it also modulates the osmolality in the heart cells and possesses strong osmotic charges (4). Contrary to cats, dogs can synthetize taurine through methionine and cysteine in their diet (5) (6), nevertheless certain diets especially grain-free and hypoallergenic ones, have been associated with cases of taurine deficiency. Different studies including the MUST-study (Multicenter Spaniel Trial) (7), the Newfoundland taurine level study (8), and the Labrador retriever grain-free study (9) discovered taurine deficiency in different dog breeds which exhibited DCM. This thesis explores the relationship between diet-related taurine deficiency and the development of DCM, highlighting the significance of taurine in canine nutrition. Over the last two years the University of Veterinary Medicine in Budapest treated at least 3 dogs experiencing dilated cardiomyopathy with taurine deficiency. While differing in breed, age, stage of the disease and taurine level all three dogs consumed a special hypoallergenic diet and exhibited taurine deficiency which improved or even recovered when supplementing taurine. Through a detailed review of the literature and case studies, this thesis aims to deepen our understanding of diet-related cardiomyopathy in dogs and the role of taurine in preventing heart disease.

DCM Pathophysiology, Histopathology, Breed predisposition

One of the most common causes of sudden cardiac death in dogs is the structural cardiac disease “dilated (or congestive) cardiomyopathy” (DCM) (10).
DCM encompasses conditions marked by systolic pump failure and ventricular cavity dilation (11). Its course can be split in two phases, the preclinical and the clinical phase (12). First there are no clinical signs, but on echocardiography visible changes can be seen like the enlargement of the heart (13) (14) (15). Inflammation is either non-existent or very minimal, with varying levels of fibrous tissue and small patches of muscle cell degeneration present (14) (15). Advancement to congestive heart failure (CHF) typically happens under two to three years after the preclinical phase is identified (16). Compensatory mechanisms collaborate to preserve cardiac output and prevent the onset of CHF (12).
Meanwhile the sympathetic activity increases, associated with rising levels of catecholamines, especially norepinephrine (17). The high plasma catecholamine levels released by adrenergic cardiac nerves, improve cardiac contractility (positive inotropic) and increase the heartbeat (positive chronotropic) (18). Conversely, this reaction is also a burden for the heart as it increases the amount of work and may speed up the death of myocardial cells (19). The degree of left ventricular dysfunction and the risk of death are directly linked to the level of elevated plasma norepinephrine concentration (18) even in asymptomatic DCM dogs (20). Symptoms of dogs suffering DCM at presentation include dyspnoea arising from pulmonary oedema but also pleural effusion, as well as dilatation of the belly due to ascites (21) (22), which are already signs of CHF (22) (23).

Electrocardiographic irregularities are often seen in dogs with DCM, although they are not unique to this disease (16). As one of those, atrial fibrillation (AF) is the most often identified (24) (25) (21) (22) (26). Yet, ventricular premature depolarizations and ventricular tachycardia have been discovered predominantly in Dobermann Pinschers (27) (28).

Often, the cause of the disorder remains unknown, leading to its classification as "idiopathic" (11). In other cases, congestive cardiomyopathy is associated with exposure to toxic agents, and nutritional deficiencies (14) (15). It is proven that breeds like Dobermanns, Boxers, Irish Wolfhounds, Newfoundlands, Welsh Springer Spaniels but also Cocker Spaniels and Portuguese Water Dogs have a genetic predisposition for DCM and they show different gross histopathology types (2) (29). Besides in the Database of the Purdue University, the Great Dane, the Labrador Retriever, the American Cocker Spaniel and the Golden Retriever were the most common DCM patients between 1981-1991 (30). In Dobermanns and Boxers only

the fatty infiltration type has so far been documented whereas the attenuated wavy fibre type presents in many breeds though still predominantly affecting giant-breed dogs (2).
Dogs with the fatty infiltration type of myofiber pattern may display myofiber degeneration, myocytolysis, and atrophy of cardiomyocytes (31). This form commonly exhibits histopathological features such as vacuolar degeneration of myofibers, atrophic myofibers, fatty infiltration, and increased collagen deposition (31) (32).

The right atrium and ventricle are the primary targets of the attenuated wavy fibre type (2) where it shows coherent myofiber atrophy (33). Indeed, it has been discovered in conjunction with the fatty infiltration type (34) (35). Attenuated wavy fibres being present proposed an early indicator of DCM generation (31). The substantially reduced size of these wavy myofibers (less than 6 µm compared to 10-20 µm in healthy controls) leads to a left ventricular wall that may be up to half the normal thickness that can be seen in healthy controls (31). The last phase of DCM presents itself with the symptoms of CHF, which offers only a poor prognosis (2).

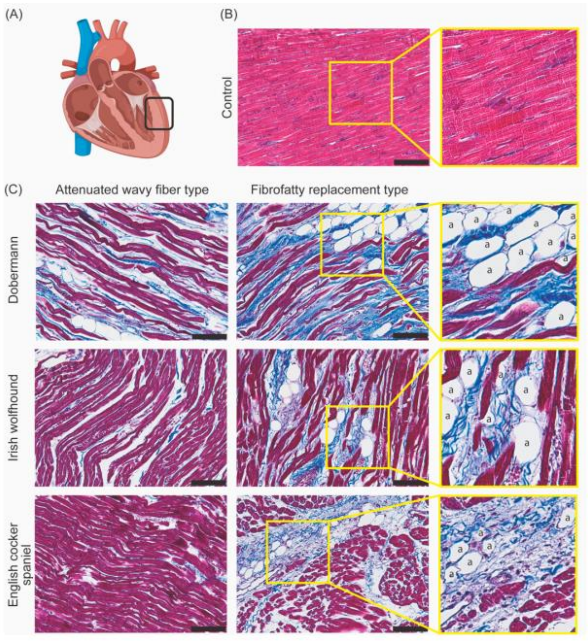

Figure 1

"Histologically distinct forms of canine DCM. Masson's trichrome staining of 4 µm thick paraffin embedded slides [39]. (Red = cardiomyocytes, blue = fibrotic/connective tissue, a = adipocyte, Animals 2022, 12, 1679 5 of 18 black scale bar = 100 µm). (A) Model of the heart showing the location (depicted in the black box) of the collected tissue in the left ventricle. (B) Control tissue (3-year-old male Beagle with no cardiac symptoms) showing healthy cardiomyocytes. (C) Diseased tissue (4-year-old male Dobermann, 5-year-old Irish wolfhound, and 7-year-old English cocker spaniel) showing the attenuated wavy fibre type and fibrofatty type in three pathologically confirmed DCM cases." (2)

Diagnosis

The diagnosis of DCM is frequently carried out by echocardiography and a 24 h electrocardiography (ECG) (36) (37) (38). In cases where there are no changes in size and contractility the 24 h ECG can show extra ventricular systoles which are considered to be a Cutt-off for occult Dobermann-cardiomyopathy if over 50 in 24 h (39). Despite offering only

a single-dimensional view and being performed in a minor section of the ventricle, the M-mode has been regarded as the gold standard for identifying ventricular morphometric changes in patients with DCM (40).
In this one dimension the Teichholz formula is a practical tool for evaluating the size of the heart and the ejection fraction of the chambers (28), which is the percentage of the blood volume which exits one chamber compared to the total capacity of such chamber.

There is a wide age range when clinical signs first present, nevertheless it sets around 5-7 years (16). Age is also a common risk factor for upcoming heart diseases (41).

Sex predisposition

Interestingly DCM seems to occur more often in males than in females. Already in 1992 O'Grady & Horne discovered the male prevalence in Dobermann Pinschers (42). In a study of 500 Irish Wolfhounds, males were hit by a considerably higher prevalence of DCM than females (23). M. W. S. Martin (2009) examined 369 cases of DCM in which males were visibly more affected than females in the most widespread breeds (13).

With an incidence of around 60%, also human males appear to be more affected by DCM than females, although it is acquired autosomal dominant (43). They even have a worse long-term prognosis (44) and higher mortality rate with higher and earlier occurrence of symptoms than females (45) (46) (47).

Supplementary dietary recommendations in treatment

In the therapy of cardiac diseases there are many supplements which may have a beneficial effect on cardiac health, but only some are proven to have an actual impact. Antioxidant supplementation may have a beneficial effect in dogs, but further research is needed to prove its impact in heart disease therapy.

Antioxidants

In heart diseases oxidative stress arises when Reactive oxygen species (ROS) surpass the available number of antioxidants, which would, in healthy conditions, neutralize them (48). Such ROS, characterized by an unstable molecule with a single unpaired electron, can trigger a chain reaction of oxidative detriment affecting cellular lipids, proteins, and DNA (48). In diseased hearts, the efficiency of mitochondria decreases, leading to increased production of ROS (49). If the levels of available antioxidants are even lower, measuring high oxidized

glutathione, oxidative stress becomes worse (50) (51).
Hence refilling the body with high quantity of antioxidants counteracts the degenerative process of oxidative stress. This can be Vitamin E, Vitamin C or taurine, which is also profitable for the heart itself (48).
As one of those, using vitamin C in humans as a preventative measure decreased the risk of atrial fibrillation by an average of 27% (52), which is a common electrocardiographic irregularity in DCM in dogs (21).

Coenzyme Q10

Coenzyme Q10 also possesses antioxidant properties and is essential for energy production (53). Various mechanisms suggest that coenzyme Q10 could be significant in cardiac disease, which is why some researchers have speculated that a lack in Q10 might even cause DCM (54). Vice versa the addition of Q10 in the diet could address a deficiency, improve myocardial metabolic efficiency, and boost antioxidant defence (54).

Omega 3 poly unsaturated fatty acids (PUFAs):

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are long chain n3 PUFAs, aid in easing the inflammation linked to heart failure (55) (56). Eicosanoids, which play a crucial role in mediating inflammation, come from the 20-carbon n6 PUFA (arachidonic acid) or EPA (48). While eicosanoids derived from arachidonic acid are typically classified as proinflammatory mediators, they are essential in modulating the immune response via intricate interactions with leukocytes and play a vital role in the initial phase of inflammation (56). Yet, an overload of these Eicosanoids can lead to an inflammatory disturbance (48). Eicosanoids originating from EPA are viewed as less inflammatory or potentially anti-inflammatory relative to those produced from arachidonic acid (48). Another anti-inflammatory effect of n3 PUFAs can be seen by the downregulation of special inflammatory receptors, which lead to a decrease of inflammatory mediators and lessens fibrosis of the heart and remodelling (55) (56).
In dogs, adding n3 PUFAs to their diet decreased the likelihood of atrial fibrillation and secondary atrial fibrosis in experimental models, as well as reduced ventricular arrhythmias in Boxers with cardiomyopathy of natural origin (57) (58). Dogs with heart failure that were given fish oil, a source of n3 PUFAs, exhibited a decrease in inflammatory mediators and cardiac cachexia improved; however, there was no enhancement in survival time (59). Nasciutti et al describe in their study with 29 dogs a decrease in volumetric overload,

antiarrhythmic benefits (decreased chance of establishing arrhythmias by 2,96 times), and protection from aggravation of dogs with B2 and C stages of MMVD (60).

Sodium:

In human patients it has been practice reducing sodium intake to achieve lower blood pressure and so avoid hypertension (61). Nevertheless, recent studies demonstrated an activation of the RAAS system and a higher mortality, while having minimal effects on the blood pressure when restricting sodium (62). Comparable to humans, in dogs avoiding sodium in the diet induces the RAAS system and may even provoke cardiac and vascular alterations (63). Hence, neither excessively higher nor much lower intake of sodium has been proven to have significant benefits.

Potassium:

The mineralocorticoid antagonist spironolactone and angiotensin-converting enzyme inhibitors, used in CHF therapy, leaves out potassium excretion, so excessive supplementation may lead to hyperkalaemia (48). Conversely, hypokalaemia can develop in anorectic animals through furosemide, which is the most established diuretic in CHF, due to the fact that it boosts secretion of potassium as well as sodium (48). At the moment the only time of addition or limitation of potassium should be, if there is a clinical indication (like a deficiency or surplus) (64).

L-carnitine

Levocarnitine (L-carnitine) is an amino acid derivate and not an amino acid, therefore it is not involved in the protein synthesis (65). Carnitine in the body is stored in the cardiac and skeletal muscles mostly (66) where it exists in three forms: free carnitine, short-chain acylcarnitine, and long-chain acylcarnitine, which is attached to a fatty acid (67). This is important for the heart, as it oxidizes long-chain fatty acids for 60% of its energy production (68) inside the mitochondria (67). Carnitine also has a buffering nature (69) and can act as a detergent inside the mitochondria; hence it contributes to its detoxification (67). Dogs can take up carnitine through their diet or even synthetised internally within the liver from methionine and lysine, essential precursor amino acids, with the help of iron, vitamin C, and vitamin B6 as necessary cofactors (67) (70).

Role of Taurine

Taurine is a free amino acid (not bound into proteins), which contains sulphur and occurs in a substantial number in the body, especially in the cardiac muscle, skeletal muscle, nervous tissue, and thrombocytes. (67). The complex role of taurine is not fully understood, but among other things, it conjugates bile acids and detoxicates foreign substances, which are excreted in bile (3) (71). Additionally, it takes part in the retinal function and development of nervous tissue, with stabilization of their membranes, and has antioxidant activity, reduces thrombocyte aggregation and supports normal function of reproduction (71) (72) (73) (74) (75) (76) (77) (78). Other than that it is known to have an elemental role in the normal function of the heart, whereupon the exact mechanism is yet to be discovered.

For cats taurine is an essential amino acid, whereas dogs can synthesize it sufficiently (5) from methionine and cysteine in their diet (6). Consequently, insufficient supplementation of taurine will lead to a systemic deficiency and further to DCM in cats (79). Research in taurine-deficient animal models suggests that taurine is a vital nutrient for proper development, growth, and the maintenance of physiological functions across various tissues, not only during foetal and neonatal stages but also throughout growth, adulthood, and aging (80) (81). For example, cats that were fed a casein diet only presented retinal degeneration later (72). Taurine transporter knockout mice had a reduced fertility and also degeneration of the retina (82). Raising monkeys Hayes et al discovered that feeding only soybean infant milk formula without taurine led to substantially decreased growth (83).

The detailed function of taurine on the heart cells is unclear, nevertheless it is suspected to influence the calcium concentration in the tissue and its disposability (3) (84) (85). Besides, it has an antioxidant activity (inactivation of free radicals) and modulates the osmolality in the heart cells in order to protect the heart (4). Furthermore, specialist suspected that differences in the concentration intracellularly have a significant effect on the protection of the heart and nervous tissue, because of the strong osmotic charge (4). Other presumptions include the N-methylation of the phospholipids of cell membranes (86) and influences on contractile proteins (87) (88). As taurine is a physiological angiotensin-2-antagonist it is suspected to react mutually with the Renin-Angiotensin-Aldosterone system (67) (89).

Metabolism/Synthesis of Taurine:

The taurine-specific transporter, known as TAUT (SLC6A6), plays a key role in the exogenous transport of taurine (90). It facilitates taurine absorption in the intestines, uptake across the plasma membrane, and transport across the placenta (91) (92) (93) (94).

Taurine is synthesized through the metabolism of hypotaurine or cysteic acid, both of which are derived from cysteine sulfinic acid (CSA) (90). This occurs as a result of cysteine being processed by cysteine dioxygenase (CDO) in the final stage of the sulphur-containing amino acid metabolic pathway, which involves methionine and cysteine (95). After cysteine is oxygenated by CDO, CSA undergoes further oxidation by CDO and is converted to cysteic acid (95). Cysteic acid is then decarboxylated by cysteine sulfinic acid decarboxylase (CSD), leading to the production of taurine (90). Alongside this, CSA can also be decarboxylated directly to hypotaurine by CSD (90). Hypotaurine is then oxygenated to form taurine (90). The conversion of hypotaurine to taurine involves the enzyme NAD-dependent hypotaurine dehydrogenase, which functions without oxygen (90). The hypotaurine pathway is thought to be the dominant process for taurine production, primarily due to the fact that cysteine sulfinic acid decarboxylase (CSD) has a stronger preference for cysteine sulfinic acid (CSA) over cysteic acid (96) (97). The exact enzyme responsible for this oxygenation reaction is still poorly understood, as hypotaurine dehydrogenase has not been purified to date (90).

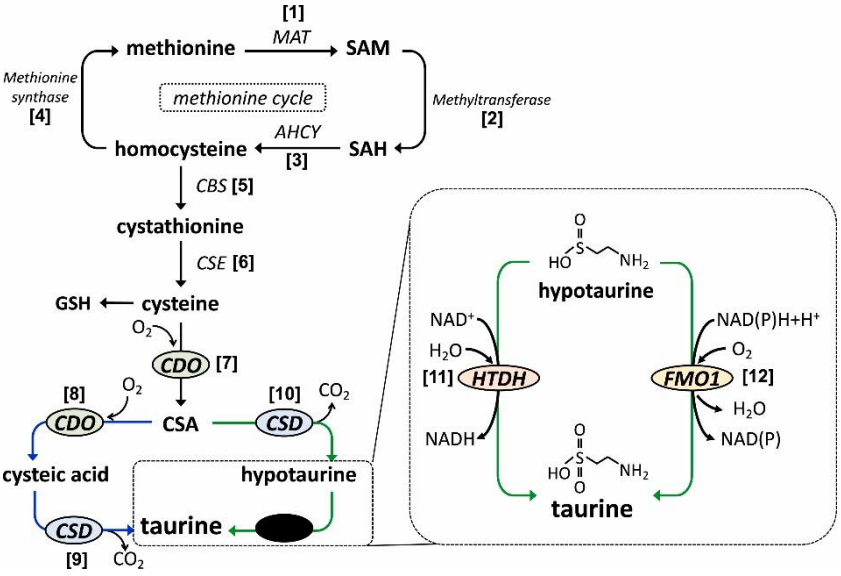

Figure 2*"The taurine synthesis pathway in mammals." after Miyazaki, T. (2023)* (130)

Additionally different hormones regulate the taurine synthesis. In the rat increased thyroxine, and a lack of an adrenal gland leads to a depressed taurine synthesis in the liver and in other tissues (98) (99). Whereas increased sex hormones like testosterone brings CSD to be upregulated (100).

Taurine Deficiency in cats

A key step in taurine synthesis involves the decarboxylation of cysteinesulphonic acid to hypotaurine, which is then oxidized to taurine (101). In cats, however, this decarboxylation

process has very low activity, meaning they are unable to convert sufficient cysteinesulphonic acid into taurine (102) (103). Consequently, cats are more prone to taurine deficiency due to their limited capacity to synthesize taurine from available precursors (102) (103). Unlike other animals, cats rely solely on taurine to conjugate with bile acids, making taurine an essential nutrient for them (104) (101). This exclusive use creates an obligatory requirement for taurine in their diet (104). Over 30 years ago taurine deficiency was the most prevalent (79), but nowadays it is rarely seen, considering the supplementation of taurine to cat food henceforth (105). If it is discovered at the present time, a taurine deficiency through homemade diets or a one-sided diet with only chicken for example is being suspected to be the cause (105). A straightforward treatment with taurine administration is likely to cure this heart disease (79) with visible improvement on the echocardiogram after 2-3 months (105). Cats which present with taurine-deficiency-related DCM, most often show signs of left heart failure, i.e. pulmonary oedema and/or pleural effusion, just like in dogs and cats with other cardiomyopathies (106) (105). Other clinical signs seen are an increased respiratory rate, difficulties to breath and a lower body temperature, due to low perfusion (also detectable on cool paws and ears) (107) (105). Furthermore, Sturman et al showed that cats who consumed a taurine-free diet developed fertility issues and retinal degeneration (108).

Taurine and Aging

Singh et al discovered that in humans with increasing age the taurine level decreases (109). Therefor the taurine supplementation has been inquired in mice with positive effects on the life span by an 10% increase compared to the control group (109). They also seemed healthier and had greater strength and muscle endurance (110). By blocking the “Slc6a6” (sodium- and chloride-dependent taurine transporter) mice experienced a radical decline of longevity (109) (111). Conversely when counteracting this blockage their lifespan rose proposing a connection between cell senescence and taurine deficiency (109). Sirtuins are a group of proteins involved in regulating various signalling pathways that provide information about the organism's metabolic condition (112) (113). As organisms age, the expression of sirtuins declines, while their activation or overexpression has been linked to enhanced longevity (114) (115). When supplementing taurine seemed to promote the SIRT1 activity and in conjunction prevent malfunctioning of organs (110). Recently Kriström et al also confirmed in their “Cure project” that the examined dogs exhibited decreasing taurine levels with increasing age (116).

Hypoallergenic Diets and taurine deficiency

As interest in alternative protein sources grows, insects have emerged as a promising high-quality feed option. Recent studies have evaluated the taurine content in various commercially available insect species, revealing that taurine levels can vary significantly between species (117). One study measured taurine levels in ten insect species by using an electrophoretic method (117). *Gryllus assimilis* (commonly known as the field cricket) exhibited the highest taurine concentration of all examined species, with 121.0±10.2 mg per 100 g of fresh weight and 436±34 mg per 100 g of dry matter (117). In contrast, *Schistocerca gregaria* (the desert locust) had the lowest taurine content, with only 5.4±0.6 mg per 100 g of fresh weight and 15±2 mg per 100 g of dry matter (117). This variability in taurine levels across insect species shows that some insects, like *G. assimilis*, offer taurine levels comparable to traditional feed sources (such as fishmeal and animal tissue), while others may provide insufficient taurine for animals reliant on dietary intake (117).

Lamb and rice diets are commonly found in cases of described diet-related DCM. Fascetti et al suspected that in the 12 cases they examined the lamb meals may have been of low quality and therefor have a decreased bioavailability of sulphur amino acids (the precursor of taurine) (118). Besides, lamb meal was found to demonstrate an impaired digestibility in the ileum in dogs concerning the nitrogen and cysteine content (119). This leaves another cause for the detected taurine deficiency- poor quality and therefor low bioavailability and a poor digestibility in general of this type of meat.
Rice in contrast could also contribute to the discovered lower taurine levels by increasing the excretion of bile acids through its moderately soluble fibre and high fat content (118).

Taurine-deficiency in dogs with DCM

Taurine is not considered essential in dogs, yet Kramer et al investigated 1995 the taurine plasma levels in dogs with DCM and chronic degenerative mitral valve disease and discovered a deficiency in 17% of 75 dogs having DCM (120). Those breeds were not the most common ones associated with DCM, but Golden Retrievers and American Cocker Spaniels (120).

MUST (Multicenter Spaniel Trial) Study

1997 Kittleson et al administered taurine and L-carnitine supplements to two American Cocker Spaniels suffering from DCM and those dogs showed a positive response (7). After

that they started the MUST study to evaluate whether the American Cocker Spaniels have low plasma taurine or carnitine concentrations and if adding them shows a positive reaction (7). All dogs showed initially low plasma taurine concentrations (<50nmol/mL) but rose remarkably (357 +/- 157 nmol/mL) when added to their diet. In contrast, the placebo group stayed below 50 nmol/mL at any point. The plasma carnitine levels also were within the normal range in the beginning and in the placebo group (29 +/- 15 mmol/L) but rose as well remarkably in 11 dogs to 349 +/- 119 mmol/L when added to their diet. On the echocardiography the placebo group showed no differences, whereas the supplementation group showed a substantially decrease in the mitral valve E point-to-septal separation and the left ventricular end-diastolic and end-systolic diameter. Also, the fraction shortening (FS) rose drastically but could not reach the physiological span. Once the dogs showed an improvement in the echocardiography their medications (furosemide, ACE-inhibitors, digoxin) were set off. The dogs lived for at least 14 +/- 7 months when they were older than 10 and even for 46 +/- 11 months when they have not reached the 10^{th} year yet. They concluded that American Cocker Spaniels suffering from DCM also experience taurine deficiency and correspondingly react positively to the supplementation of taurine and carnitine. So much they could even stop the DCM therapy and retain a normal quality of life.

Newfoundlands taurine level study:

2006 Backus et al investigated the correlations in plasma taurine concentration with cysteine and methionine concentrations and the amount of the taurine de novo synthesis in 216 Newfoundlands (8). It was not only in small breed dogs like the cocker spaniels, but also in large breed dogs like the Newfoundlands that taurine deficiency was found, so body size may play an essential role in the pathogenesis (8). 2003 Tôrres et al measured the plasma and skeletal taurine concentrations in dogs of different size and found out that the larger breeds (36 +/- 1,8 kg) and mixtures have an essentially lower taurine concentration than the smaller beagles (12 +/- 0,5 kg) being on the same diet (121). As a consequence, Tôrres et al. proposed that dogs' dietary need for sulphur amino acids increases at a different rate than their metabolizable energy (ME) demands (122). Therefor Backus et al examined the big breed Newfoundlands, which have a tendency to establish DCM (123).

The study observed a wide range of taurine concentrations in both blood and plasma, with values showing a normal distribution. The average taurine concentration in blood was 226 ± 57 mmol/L, and in plasma, it was 81.1 ± 34.9 mmol/L and low (<= 40 mmol/L) in 8% of the dogs. As a result, they could summarize that the dogs with lower plasma taurine

concentrations (<= 40 mmol/L) were older, less active, had more health problems which also needed medications. 3 of 9 taurine-deficient examined dogs showed ventricular enlargement and fraction shortenings (<22%) similar to DCM and when given taurine supplementation for 4 months (1g twice daily) the fraction shortenings changed from 15 +/- 14 to 37 +/- 6%. Furthermore for 3 weeks they fed a diet which is known to be sufficient in sulphur amino acids (5.4 g/kg) to 6 Newfoundlands (52.5 +/- 2,3 kg, 3.5-7y) and 6 Beagles (13.2 +/- 2.3 kg, 5.5y) and received following results. The Newfoundlands exhibited lower plasma taurine levels (49 +/- 16 vs. 97 +/- 25 mmol/L), cysteine and blood glutathione, as well as a decreased de novo taurine synthesis and higher faecal bile acid excretion. This indicates that Newfoundlands have a greater dietary requirement for sulphur amino acids compared to Beagles. Consequently, when their intake of these amino acids is insufficient, they may develop deficiency-related conditions such as DCM. However, this condition can be reversed with taurine supplementation.

Labrador retriever grain-free study

2022 Bakke et al initiated a study with healthy Labrador retriever dogs to investigate the influence of a grain-free high legume diet for 30 days (9). Samples of blood and urine were taken initially and on days 3, 14, and 28/30, then assessed for haematological values, clinical biochemistry, and taurine levels. After 28 days of feeding the test diet, there were progressive and significant reductions ($p < 0.001$) in red blood cell counts (RBC) (7%), haematocrit (8,3%), and total haemoglobin (6,3%), along with a 41.8% rise in plasma inorganic phosphate levels. Those findings coincided with those of clinical DCM cases. Regarding taurine, on day 14, the test dogs showed a temporary rise in whole-blood (23.4%) and plasma (47.7%) taurine levels, while by day 28/30, taurine: creatinine ratios in fresh urine and taurine concentrations in pooled urine had decreased by 77% and 78%, respectively. Therefor a co-dependency of taurine concentrations and the diet may explain the rise in DCM of non-typical breeds.

Certain breeds with taurine related cardiomyopathy

Although breed specificity is not fully understood genetics may play a significant role in development of taurine deficiency in dogs. For instance, certain breeds may have altered taurine metabolism or inefficient absorption from the diet, increasing their need for dietary taurine. Basili et al analysed the taurine levels of 16 English Cocker Spaniels with DCM of which 13 had a decreased plasma taurine level (<50 µmol/L) (124). They experienced a change in left ventricular systolic function and left ventricular dimensions for the better

through taurine supplementation (124). In addition to those cases, 53 of 180 examined English cocker spaniels of the recent so called “CURE project” (Canine taURinE) showed low taurine levels and further 13 of those 53 had even clinical and radiographic signs of CHF besides visible echocardiographic changes (116). 62 of all examined English Cocker Spaniel consumed red meat (lamb, beef, pork, reindeer, and venison) at least 3 months before the trial and their taurine concentrations were significantly lower than of those consuming white meat (poultry and fish) so a clear correlation between diet and taurine deficiency could be found (116). Even the age showed peculiarities as dogs with decreased taurine levels were found to be older than those with normal taurine levels in the blood (116). Also, the here described English Cocker Spaniel, patient of the university of veterinary medicine in Budapest, stands in line with the two studies mentioned above as he is of the breed suspected to be prone to taurine deficiency, and exhibited a taurine deficiency after consuming a hypoallergenic diet which improved with taurine supplementation.

The common ancestor of taurine related cardiomyopathy

Interestingly the Newfoundland dog, the Labrador Retriever and the English Cocker Spaniel share some history. Starting in the 15th century fishermen and colonists brought different dog breeds to Newfoundland (125). The French Fishermen brought Pyrenees-type dogs with a strong, loyal character and had thick coats suited for cold climates (125). Whereas the English settlers brought Curly-Coated Retrievers with black fur and a smaller statue known for their intelligence and hunting skills (125). Over time those dogs were bred together and new breeds evolved including the Newfoundland, the Landseer (a type of Newfoundland), and the Labrador Retriever (125). Later written records say that in 1700’s the so-called St. John’s water dogs were imported by trading vessels from Newfoundland to Labrador, Canada and became very appreciated by helping fishermen

Figure 3 *St. John’s Water Dog (132)*

Figure 4 *The English Water Spaniel “Quaille”, 1797, by Henry Bernard Chalon (131).*

to catch fish which wriggled off their hook (126). They were further exported to Britain where they were called Lesser Newfoundland dogs (127). The Earl of Malmesbury admired these handy dogs very much and started breeding them, giving them the new name Labrador Retrievers (127). It is unclear whether those St. John's water dogs are the origin breed of the Labrador and the Newfoundland as well, but later the gene pool of the Labrador Retrievers became so narrow that the Newfoundland dogs and Spaniels became a practical breed to be crossed in to maintain their positive attributes (128).

Lastly genetic research showed that the Curly Coated Retriever (origin of the Lab and Newfoundland) and the Irish Water Spaniel are very close related (129). The Curly Coated Retriever originally seems to be a cross between the St. Johns water dog and the English Water Spaniel (129). As their story goes far back in history it is possible that this breed is the origin of a genetic influenced taurine deficiency susceptibility. Despite their differences in size and usage the three breeds, Labrador retriever, Newfoundland and English Cocker Spaniel share some genetics through their common history, and they are all working and retrieving breeds.

The common genetic heritage could contribute to similar genetic traits like a predisposition to taurine deficiency which may impair taurine metabolism or absorption in some breeds. Additionally, their shared high energy and endurance tasks might make them more prone to any inherited inefficiency in taurine synthesis or utilization which leads them to develop dilated cardiomyopathy. Especially when taurine levels are compromised through the diet.

Cases

Over the last 2 years the University of Veterinary Medicine in Budapest had at least 3 different cases of taurine deficiency in breeds normally associated with DCM, who endured a dilation of the heart which could be mildened by the supplementation of taurine among other medications. They differed in Age, Sex, Breeds, stage of the disease and taurine level, but all received a special hypoallergenic diet for at least 1 year before developing signs of DCM.

The scheme for finding the diagnosis included ruling out any other cause for DCM besides idiopathic source. Myocarditis could be excluded by measuring Troponin-I which is highly elevated in those cases. Other reasons like cardiotoxic agents have to be ruled out by troponin and BNP/NT-proBNP biomarkers or cancerogenic origins by imaging methods i.e. Knowing the nutritional background of the dog can rise suspicion for finally assessing taurine levels, which can aid in reaching an accurate diagnosis before attributing the condition to idiopathic dilated cardiomyopathy.

Taurine concentrations were determined from EDTA-plasma samples, which required freezing before being sent to the laboratory for analysis. The reference ranged from 5,1 to 12,1 mg/L.

Case 1- Newfoundland:

A 6-year-old male Newfoundland dog presented with clinical signs consistent with heart failure, including a heart rate of 200 beats per minute and marked cardiac dilation with atrial tachycardia observed on echocardiography (fraction shortening (FS): 11,5%). Initial testing ruled out myocarditis, as Troponin-I levels were not elevated to the extent typically seen in such cases. Upon reviewing the dog's dietary history, it was noted that it had been on a hypoallergenic lamb and rice-based diet for two years, raising concerns. Subsequently, whole blood and taurine levels were measured, revealing significant taurine deficiency (0.49mg/L), while all other blood parameters remained within normal limits. The dog was treated with Diltiazem, Digoxin to counteract atrial fibrillation and Pimobendane and Furosemide as heart therapy for DCM/heart failure.

To address the deficiency, taurine supplementation was initiated at a dosage of 150 mg/kg twice daily. Methionine, a precursor amino acid for taurine synthesis, was also administered. Following these adjustments to the treatment plan, the Newfoundland dog reached a heart rate of 120 beats/minute and survived an additional two years before succumbing to heart failure.

Taurine levels were not re-evaluated, as current methods only allow for measurement of blood concentrations and not taurine levels within heart tissue in a living animal.

Case 2 – Labrador:

A 7-years-old male Labrador presented with symptoms of coughing and exercise intolerance. On the echocardiography it became visible that given symptoms rose from significantly enlarged heart chambers, left and right heart failure, reduced aortic and pulmonary outflow velocity, reduced contractility, with a FS of 24% and the presence of ascites. Despite initiating standard therapy for dilated cardiomyopathy (DCM) with Pimobendane, Furosemide, and ACE inhibitors, there was no noticeable improvement over two years. In fact, the condition worsened, with the FS decreasing to 15%. Upon testing, the taurine level was found to be low at 4.34 mg/L, consistent with the dog's diet history of consuming a hypoallergenic diet based on insects and peas for one year. Remarkably, the introduction of taurine supplementation alongside the ongoing heart failure therapy led to improvements. The FS increased to 19%, and the heart rate dropped from 136 beats per minute to 74 beats per minute. The ECG remained normal throughout. Unlike the previously mentioned Newfoundland case, this Labrador showed a more stable condition, with taurine supplementation improving cardiac contractility, quality of life, and life expectancy. However, while cardiac function can be enhanced, the irreversible damage to the myocardium cannot yet be completely restored.

Case 3 – English Cocker Spaniel:

A 7-years-old male English Cocker Spaniel was cardiologically examined because of the "sudden" presence of a heart murmur. Before the dog was frequently auscultated and only recently a systolic heart murmur of 3/6 could be witnessed. Otherwise, the dog was asymptomatic. On the echocardiography signs of cardiomyopathy could be seen, a dilated left side of the heart, a decreased contractility, but the heart was in compensated state and had a heart rate of 80/min. Sensitized by previous cases the dietary history was asked and revealed a hypoallergenic diet of "Trovet" for a year and concurrently a taurine level of 2,79 mg/l. "Trovet" has different kind of hypoallergenic diets, deer, grain free, insects, lamb and rice and more. He was set on Pimobendane and taurine supplementation immediately and controlled three months later. The Cocker Spaniel underwent a follow-up echocardiogram, which revealed completely normal results. This indicates that after three months of taurine supplementation, the condition has successfully reversed. We have now begun tapering off the

other medications, although continuing the taurine supplementation for an additional three months is recommended, given that the dog is now on a regular diet. Should the dog be placed on a specialized diet in the future, continued taurine supplementation is highly advised. In this case the taurine deficiency was caught in an early state where the heart didn't have experienced a damage yet and the effects could be reversed.

Conclusion and Discussion

In the three cases discussed, the dogs were of different breeds and at varying stages of cardiomyopathy, yet they all shared a common factor: they were fed a hypoallergenic or "special" diet and exhibited taurine deficiency at different points in their disease progression. The Newfoundland dog, which had been on this diet for two years, presented with a highly dilated heart, severe heart failure and a notably low taurine level. The extended duration of the special diet seemed to correlate with more severe cardiomyopathy and the onset of heart failure, suggesting a greater impact on cardiac muscle with prolonged dietary deficiency. Although the disease could not be fully reversed due to the advanced cardiac damage, taurine supplementation appeared to alleviate symptoms and potentially improve life expectancy.
In the second case, a Labrador showed no response to standard heart failure treatment until taurine supplementation was added. This dog had been on a hypoallergenic diet for only one year, leading to the conclusion that the shorter exposure resulted in less severe cardiomyopathy compared to the Newfoundland.
The third case supports the thesis as the dog was frequently auscultated, but only after administering the hypoallergenic diet, it exhibited a taurine deficiency (2,79 mg/L) and a decreased systolic function with a heart murmur 3/6 which could be reversed because it was diagnosed before irreversible cardiac damage could take place.
Each dog was on one kind of hypoallergenic diet, but the types and feeding durations were different. This raises the question about whether it's the specific ingredients of the hypoallergenic diets, the length of time consuming them, individual or breed differences contributes to taurine deficiency. The Newfoundland, who ate a lamb and rice diet for two years, showed more advanced cardiomyopathy, while the Labrador, fed an insect and pea-based diet for just one year, had milder symptoms. It seems that the longer a dog is on hypoallergenic diet, the more severe are the symptoms and impacts on the heart muscle although this sample size is not enough to explain any details.

These cases highlight the importance of taurine measurement when prescribing hypoallergenic diets, particularly if a young or atypical breed presents with signs of cardiomyopathy. Assessing the diet history and taurine levels could help detect deficiencies before heart failure develops and irreversible cardiac damage occurs. While the exact source of taurine deficiency in these cases remains unknown, each dog experienced improved cardiac function following taurine supplementation.

One possible reason for the unknown origin of taurine deficiency could be the lack of routine testing for taurine levels among cardiologists, particularly when patients are on hypoallergenic or "special" diets. Cardiologists may not commonly consider diet-related factors unless prompted by specific symptoms. Similarly, dermatologists prescribing hypoallergenic diets for dermatological issues may not anticipate the potential for heart-related side effects resulting from the diet, as their focus is on treating skin conditions. This gap in awareness between specialties may contribute to the underdiagnosis of taurine deficiency as a factor in cardiomyopathy.

In conclusion, the evidence gathered throughout this thesis underlines the complex connection between diet, taurine deficiency, and cardiomyopathy in dogs. Because taurine is an essential amino acid with critical roles in cardiac function, its deficiency has been linked to the development of dilated cardiomyopathy, especially in certain breeds, which seem to be more susceptible to taurine deficiency. This suggests that genetic factors may influence their ability to metabolize or absorb taurine efficiently from their diet. Diet-related taurine deficiency could be a triggering factor for further cardiomyopathy, particularly in breeds with possible inherent metabolic or genetic vulnerabilities. Further research is needed to clarify why or if some breeds are more susceptible to taurine deficiency and how diet impacts these variations.

The main conclusion in the prevention of taurine deficiency related canine cardiomyopathy is the need to make veterinarians and dog owners aware of the condition and to suggest routine testing of taurine levels after patients are put on hypoallergenic or "special" diets. The monthly cost of a hypoallergenic diet is much higher than the single laboratory test and cannot be compared to the fatal consequences of a cardiomyopathy caused by taurine deficiency.

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Statements

UNIVERSITY OF VETERINARY MEDICINE, BUDAPEST
~~founded in 1787, EU-accredited since 1995~~

INTERNATIONAL STUDY PROGRAMS
secretary, student@univet.hu

Thesis progress report for veterinary students

Name of student: ANN-MARIE WULFF

Neptun code of the student: J3MFUN

Name and title of the supervisor: Dr. Kiss Gergely

Department: Department and Clinic of Internal Medicine

Thesis title: Diet related Cardiomyopathy in Dogs

Consultation – 1st semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2024	01	25	Gathering articles	Kiss
2.	2024	02	07	Table of contents	Kiss
3.	2024	02	29	Drive creation, shared document, content discussion	Kiss
4.	2024	03	05	Answering general questions	Kiss
5.	2024	05	31	Signature, case study discussion	Kiss

Grade achieved at the end of the first semester: 5

Consultation – 2nd semester

	Timing			Topic / Remarks of the supervisor	Signature of the supervisor
	year	month	day		
1.	2024	07	23	Citations	Kiss
2.	2024	08	25	Most relevant studies	Kiss
3.	2024	09	20	Online meeting about own cases	Kiss
4.	2024	09	23	Additional data of cases	Kiss
5.	2024	11	11	Final comments about content and layout	Kiss

Grade achieved at the end of the second semester: 5

1

The thesis meets the requirements of the Study and Examination Rules of the University and the Guide to Thesis Writing.

I accept the thesis and found suitable to defence,

.....
signature of the supervisor

Signature of the student: .....

Signature of the secretary of the department: .....

Date of handing the thesis in.....28.11.2024.....

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