Association between dilated cardiomyopathy and hypothyroidism in dogs

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Abstract

It is a known fact that thyroid hormones have an influence on the heart function. Opinions on hypothyroidism and its effect on dilated cardiomyopathy (DCM) development are controversial and often contradictory. This prospective study examined the potential association between hypothyroidism and DCM in dogs. A total of 35 dogs with DCM were included in the study. Preclinical DCM was diagnosed in 18 patients, and clinical DCM was diagnosed in 17 patients, four of which were also diagnosed with hypothyroidism. There was a positive correlation between the thyroid-stimulating hormone and body weight, left atrium size and the serum NT-proBNP concentration in patients with preclinical DCM. Euthyroid dogs with DCM had higher total thyroxine values and more ventricular premature complexes than hypothyroid dogs. Although our study did not confirm a direct relationship between hypothyroidism and DCM as a possible cause, other correlations were detected that had not yet been described in veterinary medicine.

Echocardiography, thyroid disease, canines, heart disease

Dilated cardiomyopathy (DCM) is the second most common heart disease in dogs. Based on current literature, the incidence of DCM in the overall dog population is estimated to be between 0.5% and 1.3% in the United States (McCauley et al. 2020). Autosomal dominant transmission has been reported in the Irish Wolfhound, Newfoundland, and Doberman Pinscher (Dukes-McEwan et al. 2003). A genetic variant associated with DCM has been identified in the *PDK4* gene and the *TTN* gene in Doberman Pinschers (Meurs et al. 2020). Primary or idiopathic canine DCM is of unknown or uncertain aetiology, and it is the most common form of DCM (Tidholm et al. 2001; O'Grady and O'Sullivan 2004). According to aetiology, secondary cardiomyopathies are classified as drug-or-toxin induced, genetic, infiltrative, ischaemic, metabolic, nutritional, or inflammatory myocardial diseases. One of the endocrine disorders commonly associated with DCM is hypothyroidism (Tidholm et al. 2001).

Some studies describe a higher prevalence of hypothyroidism in dogs with DCM, especially in Doberman Pinschers (Beier et al. 2015). It is a well-known fact that thyroid hormones have positive inotropic and chronotropic effects on the heart (Karlapudi et al. 2012; Razvi 2019). In canine patients with a thyroid hormone deficiency, reduced left ventricular systolic function, low QRS voltages, inverted T waves, weak apex beat, and sinus bradycardia are common cardiovascular abnormalities (Beier et al. 2015). Also, in human patients with heart failure, both low and high serum thyroid-stimulating hormone (TSH) concentrations are associated with higher mortality (Razvi 2019). Furthermore, studies looking at the effect of treatment with thyroid hormones in human patients with DCM describe improvements in the heart function, as do also experimental studies in veterinary medicine (Borgarelli et al. 2001). However, opinions on hypothyroidism and its effect on DCM development are still controversial and often contradictory

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(Borgarelli et al. 2001). None of the available studies has studied the correlation of thyroid hormones with echocardiographic indices and cardiac markers. We hypothesized that patients with any stage of DCM might have a decreased thyroid function. This study aimed to identify the association of hypothyroidism in dogs with DCM and to examine the relationship between thyroid hormones with echocardiographic indices and cardiac markers. Furthermore, this study sought to determine a possible dependency between signalment, echocardiographic, and cardiac marker values and thyroid hormones.

Materials and Methods

This prospective study enrolled dogs diagnosed with preclinical and clinical stages of DCM between September 2017 and December 2020 at the Small Animal Clinic, University of Veterinary Sciences Brno (VETUNI). This study was approved by the animal protection and welfare committee of the VETUNI. Inclusion criteria were that a complete signalment was recorded, and clinical and cardiac examinations (ECG and echocardiography) were performed in all patients. Patients that did not fulfil the criteria for any stage of DCM and had ongoing thyroid therapy were excluded. Blood was collected from all patients for haematology and biochemistry examinations, determination of cardiac markers (NTproBNP and cardiac Troponin I) and thyroid function (total thyroxine [TT4] and TSH). Thoracic radiographic examinations were performed in indicated cases.

Cardiovascular examination

A complete transthoracic echocardiographic examination including 2D, M-mode and Doppler echocardiography was performed using a cardiovascular ultrasound machine (ALOKA ALPHA 7a Tokyo, Japan) with a phased array probe with a frequency of 3–5 MHz. The examination was performed on a standing patient or in lateral recumbency. An ECG examination was performed in a standing position for 5 min using a single-channel ECG machine (Seiva EKG Praktik Veterinary, Czech Republic) at 50 mm/s paper speed and 10 mm = 1 mV calibration without any sedation. All the recordings of standard bipolar limb leads (I, II, and III) and unipolar augmented limb leads (aVR, aVL, and aVF) were taken. Heart rate and arrhythmia that appeared were recorded. A scoring system with the major and minor ECG and echocardiographic criteria was used for making the diagnosis of DCM (Dukes-McEwan et al. 2003).

Laboratory tests

Haematological and biochemical analyses were done in the Clinical Laboratory for Small Animals, VETUNI Brno. For NTproBNP determination (ELISA, pipetting robot from Tecan, washer from Biotek, Teader from Tecan, IDEXX laboratories, Leipzig, Germany) values below 900 pmol/l were considered negative for heart disease; values of 900–1800 pmol/l as possible heart disease warranting further testing; and values over 1800 pmol/l were indicative of heart disease. The detection range was 250–10 000 pmol/l, sensitivity was 89–100 % and specificity was 77–86%. Cardiac Troponin I (chemiluminescence immunoassay, Immulite, Siemens Healthcare Diagnostics, IDEXX laboratories, Leipzig, Germany) was performed with a detection limit of 0.01 ng/ml. Hypothyroidism was determined according to the manufacturer's instructions (enzyme immunoassay, Immulite, Siemens Healthcare Diagnostics) in patients with a serum TT4 value below 12.9 nmol/l (reference range 12.9–51.5 nmol/l) and a serum TSH value above 0.5 ng/ml.

All patients were divided into 4 groups: Group 1 – euthyroid patients with DCM; Group 2 – hypothyroid patients with DCM; Group 3 – patients with preclinical DCM; Group 4 – patients with clinical DCM.

Statistical analysis

Shapiro-Wilk normality test was used to evaluate the distribution of parameters. Accordingly, the data were further processed as nonparametric. Spearman correlation was used to assess the association of T4 and TSH values with selected echocardiographic parameters: end diastolic volume index (EDVI), end systolic volume index (ESVI), left ventricular internal diameter end diastole (LVIDD), left internal diameter end systole (LVIDS), sphericity index (SI), fractional shortening (FS), ejection fraction (EF), E-point septal separation (EPSS), left atrium size, the ratio of the preejection period to the left ventricular ejection time (PEP/ET), heart rate; NTproBNP value, cardiac troponin I value, age, sex, body weight and breed in each DCM group (preclinical and clinical stages) and the same parameters were used for association in all patients together (preclinical and clinical DCM). We considered a value > 0.65 as significant for all groups. Significant *P* values were determined using the F significance of logistic regressions. Mann-Whitney test was used to compare echocardiographic parameters, NTproBNP value, cardiac troponin I, T4 and TSH between groups. A logistic regression test was performed to determine the thyroid hormones' role as an independent predictor of signalment, echocardiographic, and cardiac marker values. Software BioStat 2009 5.8.3.0 were used for all statistics.

Results

A total of 35 dogs diagnosed with DCM between 2017 and 2020 were included in the study. Preclinical DCM was diagnosed in 18 patients, and clinical DCM was diagnosed in

17 patients. There were 21 intact males (60%), 2 neutered males (5.7%), 8 intact females (22.9%) and 4 spayed females (11.4%). The median ages were 52.5 months (10–101) in preclinical DCM and 84 months (56–151) in clinical DCM. The median body weight was 36.5 kg in preclinical DCM and 37.5 kg in clinical DCM groups (Table 1). The breeds included in the study were Shorthaired Weimaraners (n = 21, 46%), Great Danes (n = 4, 11%), Doberman Pinschers (n = 2, 5%), Longhaired Weimaraners (n = 2, 5%), Cane Corso (n = 1, 3%), Belgian Shepherd (n = 1, 3%), Bull Terrier (n = 1, 3%), European Sled Dog (n = 1, 3%), Black Russian Terrier (n = 1, 3%), Caucasian Shepherd Dog (n = 1, 3%), Boxer (n = 1, 3%), English Cocker Spaniel (n = 1, 3%), Briard (n = 1, 3%), Leonberger (n = 1, 3%) and Pit Bull Terrier (n = 1, 3%) (Table 2). Detected arrhythmias included atrial fibrillation (AF) in seven dogs with clinical DCM, ventricular premature complexes (VPC) in five dogs with preclinical DCM and three dogs with clinical DCM, and paroxysmal monomorphic ventricular tachycardia in one dog with clinical DCM.

Table 1. Summary of information (median of age and weight, sex predisposition) in groups.

	Euthyroid dogs with DCM	Hypothyroid dogs with DCM	Preclinical DCM	Clinical DCM
Age (months)	69 (10-151)	92.5 (74-104)	52.5 (10-101)	84 (56-151)
Weight (kg)	36 (14.8-80.0)	47.25 (27-85)	36.5 (23-80)	37.5 (14.8-85.0)
Intact males (n)	17	4	9	12
Neutered males (n)	2	0	0	2
Intact females (n)	8	0	7	1
Spayed females (n)	4	0	2	2

n - Number

Table 2. Summarization of breeds (number) in groups.

Breed	Euthyroid dogs with DCM	Hypothyroid dogs with DCM	Preclinical DCM	Clinical DCM
Shorthaired Weimaraner	15	1	12	4
Great Dane	3	1	1	3
Doberman Pinscher	2	0	1	1
Longhaired Weimaraner	2	0	2	0
Cane Corso	1	0	0	1
Belgian Shepherd	1	0	0	1
Bull Terrier	0	1	0	1
European Sled Dog	1	0	1	0
Black Russian Terrier	0	1	0	1
Caucasian Shepherd Dog	1	0	1	0
Boxer	1	0	0	1
English Cocker Spaniel	1	0	0	1
Briard	1	0	0	1
Leonberger	1	0	0	1
Pit Bull Terrier	1	0	0	1

Hypothyroidism was diagnosed in four (11.4%) of the 35 dogs. All dogs with clinical DCM were intact males; the breeds were the Great Dane, Weimaraner, Bull Terrier and Black Russian Terrier. The median serum T4 and TSH concentrations were 10.95 ± 1.24 nmol/l and 1.60 ± 2.78 ng/ml (mean ± standard deviation), respectively.

Serum cardiac Troponin I > 0.06 ng/ml (reference: < 0.06 ng/ml) was found in eight patients (44%) with preclinical DCM and in 16 patients (94%) with clinical DCM. Serum NTproBNP > 1800 pmol/l was detected in three patients (18.7%) with preclinical DCM and in 11 patients (64.7%) with clinical DCM (Table 3). The precision of all tests was determined by calculating intra-assay coefficient of variation (CV) (TSH = 2.65, T4 = 0.41, NTproBNP = 1.17 and TnI = 2.22).

Table 3. Median of echocardiographic variables and median of troponin I, NTproBNP, T4 and TSH values in each group.

	Euthyroid dogs with DCM	Hypothyroid dogs with DCM	Preclinical DCM	Clinical DCM
EDVI (ml/m^2)	128 (84-241)	100 (68-134)	112.5 (84-172)	141 (68-241)
ESVI (ml/m^2)	83 (50.5-200.0)	77.5 (33-102)	69.5 (27-113)	102 (33-200)
LVIDD (mm)	56 (40-89)	59(55-65)	54.5 (40-79)	63 (47-89)
LVIDS (mm)	57 (30-80)	50 (47-51)	43.5 (30-62)	52 (39-80)
SI	1.3 (1.00-1.90)	1.15 (1.02-1.39)	1.36 (1.07-1.70)	1.16 (0.88-1.90)
FS (%)	16.8 (7-30)	16.5 (14.0-21.3)	22.1 (12.6-29.1)	15 (7-30)
EF (%)	41.00 (20.6-67.0)	41.15 (24.0-49.5)	46.00 (34.8-67.0)	32.50 (20.6-50.0)
EPSS	13 (3-40)	16 (11-24)	10 (3-20)	21 (8-40)
LA (mm)	40.0 (29-70)	41.0 (33-71)	36.5 (29-54)	43.0 (33-71)
PEP/ET	0.31 (0.23 -1.14)	0.36 (0.22-0.68)	0.27 (0.23-0.41)	0.41 (0.22-1.14)
Troponin I (ng/ml)	0.10 (0.009-8.800)	0.12 (0.08-3.36)	0.06 (0.01-0.26)	0.67 (0.05-8.80)
NTproBNP (pmol/l)	1002.0 (250-10000)	1784.5 (1247-4235)	595.0 (250-3489)	3449.5 (1003-10000)
T4 (nmol/l)	14.20 (9.0-34.7)	10.95 (9.0-11.6)	15.40 (11.6-34.7)	11.60 (9.0-27.0)
TSH (ng/ml)	0.09 (0.03-0.65)	1.60 (0.59-6.53)	0.09 (0.03-0.44)	0.19 (0.04-6.53)

DCM - dilated cardiomyopathy; EDVI - end diastolic volume index; ESVI - end systolic volume index; LVIDD - left ventricular internal diameter end diastole; LVIDS - left internal diameter end systole; SI - sphericity index; FS - fractional shortening; EF - ejection fraction;EPSS - E-point septal separation; LA - left atrium size; PEP/ET - the ratio of the preejection period to the left ventricular ejection time

A positive correlation was found between serum TSH concentrations and body weight (r = 0.65), left atrium size (r = 0.83) and NTproBNP (r = 0.71) in dogs with preclinical DCM.

Serum T4 was decreased in the group of hypothyroid dogs with DCM. Additionally, the presence of arrhythmias between groups of euthyroid and hypothyroid dogs with DCM was different. Ventricular premature complexes did not occur in the group of patients with hypothyroidism and DCM, in contrast to the group of euthyroid patients with DCM, where VPCs were found in eight dogs (26%). Hypothyroid dogs with DCM (2 cases) had AF, and two were without arrhythmias. All the above-mentioned results are descriptive due to the low number of patients included.

We did not confirm any strong relationship between thyroid hormones and other indices using the regression test. The thyroid function did not predict changes in signalment, echocardiographic, and marker values.

Discussion

This study aimed to identify the incidence of hypothyroidism in dogs with DCM and examine the relationship between thyroid hormones with echocardiographic indices and cardiac markers. This study diagnosed hypothyroidism in four (11.4%) dogs with DCM. Beier et al. (2015) examined the role of hypothyroidism on the aetiology of DCM in 175 Doberman Pinschers. Both hypothyroidism and DCM were found in 12 out of 57 Dobermans (21.1%). The results were different to our study, where a lower percentage was found. Beier et al. (2015) had a larger group of patients, however, they examined only

Dobermans. Dobermans with DCM had a 2.26 × higher risk of co-occurring hypothyroidism. Despite optimal therapy for hypothyroidism and DCM, progression of heart disease was reported (Beier et al. 2015). Based on the results of this study, hypothyroidism does not appear to play a role in the aetiology and progression of DCM in Dobermans.

Males were overrepresented, which was consistent with many other studies (Calvert et al. 1997; Tidholm et al. 2001; Petric et al. 2002; Martin et al. 2010; Wess et al. 2010; Simpson et al. 2016; McCauley et al. 2020). Most likely, it is due to the genetic background as reported in Great Danes, where an X-linked recessive inheritance is likely (Wess et al. 2010).

The Weimaraner was the most represented breed in our study. Some studies already demonstrate a higher predisposition for DCM development in Weimaraners (Dukes-McEwan et al. 2003; Simpson et al. 2015; McCauley et al. 2020). Great Danes and Doberman Pinschers were also often included in studies. These two breeds are predisposed for the development of DCM, and results are consistent with the literature (Calvert et al. 1997; Tidholm et al. 2001; Dukes-McEwan et al. 2003; Meurs et al. 2007; Martin et al. 2010; Wess et al. 2010; Stephenson et al. 2012; Beier et al. 2015; Eberhard and Wess 2020). In our study, a Great Dane was diagnosed with hypothyroidism and DCM. A previous report described two unrelated cases of hypothyroidism and DCM in two Great Danes (Phillips and Harkin 2003). Both dogs were middle-aged males and treated with digoxin, diltiazem, furosemide, lisinopril and levothyroxine. This study found a significant improvement in myocardial contractility, increased FS, reduced left atrial size, EDVI and ESVI after initiation with levothyroxine in dogs with hypothyroidism and DCM. These improvements persisted after the discontinuation of digoxin and lisinopril. Since the patient died soon after diagnosis, the clinical condition and treatment effects could not be monitored. Another study by Stephenson et al. (2012) examined 55 Great Danes with DCM. None of them had coexistent hypothyroidism. It is unknown if the findings of DCM in conjunction with hypothyroidism are coincidental in this breed or not. Further studies are needed.

We found a positive correlation between serum TSH and body weight in dogs with preclinical DCM. A higher TSH value can be expected with a higher body weight, which may be related to a higher prevalence of hypothyroidism seen in larger breeds (Graham et al. 2007).

In this study, a positive correlation was found between serum TSH and the left atrium size in patients with preclinical DCM. Dogs with a larger left atrium had higher serum TSH concentrations. Since the large left atrium size is a predisposing factor for developing congestive heart failure, this result may be of importance (Dukes-McEwan et al. 2003). High or low serum TSH concentrations are associated with higher mortality in patients with heart failure in human medicine (Perez et al. 2014; Razvi 2019). One human study observed a significant difference between NTproBNP values and serum TSH in patients with hypothyroidism, similar to this study. Differences in higher natriuretic peptide concentrations in hypothyroid patients were explained because they were in worse heart failure and not directly due to reduced thyroid function, and this is also possible in our small group of patients (Perez et al. 2014).

In this study, dogs with DCM and hypothyroidism had significantly lower serum TT4 values than euthyroid patients. Not all patients with DCM had low serum T4 in our study. Therefore, the euthyroid sick syndrome can lead to misdiagnosis. The survey by Beier et al. (2015) noted a reduced concentration of serum TT4 in 14 healthy dogs and seven dogs with DCM, in which confirmatory thyroid function tests ruled out hypothyroidism. We also noticed a reduced serum TT4 in our patients, but serum TSH concentrations were normal. Decreased serum TT4 and normal serum TSH were seen in three patients (16.6%) with preclinical DCM and 8 dogs (47%) with clinical DCM. Due to these results, serum

TT4 and TSH should be measured together and avoid misdiagnosis by evaluating only serum TT4 values.

Arrhythmia occurrence was different between the DCM groups. We detected the presence of VPCs in the euthyroid DCM group. Surprisingly, we did not detect this type of arrhythmia in any group with hypothyroidism. Interestingly, AF was present in two out of four patients with hypothyroidism and DCM. The most often reported arrhythmias in hypothyroidism are VPCs and ventricular tachycardia (Karlapudi et al. 2012; Beier et al. 2015), which contradicts our findings. Beier et al. (2015) did not find a significant difference in the number of VPCs/24 h between healthy and hypothyroid subjects and between DCM alone and DCM and hypothyroidism. A few case reports described the coexistence of hypothyroidism and malignant ventricular tachyarrhythmias in humane medicine. This may be due to prolonged QT interval due to bradycardia, a common finding secondary to hypothyroidism (Pechter and Osborn 1985; Beier et al. 2015). However, the study by Gerritsen et al. (1996), concluded that the frequency of primary hypothyroidism in dogs with atrial fibrillation was higher than in healthy dogs, which was also seen in our study. However, we assume that the occurrence of AF in our study may be due not only to hypothyroidism but also to DCM as another author claims (Beier et al. 2015). Hypothyroidism-associated arrhythmia did not disappear after initiating therapy with levothyroxine in reported studies (Karlapudi et al. 2012; Beier et al. 2015).

A number of limitations influenced the results of our study. Mainly, our study included a small number of dogs with co-occurrence of DCM and hypothyroidism, which is why the interpretation of our results should be done cautiously. Presence of arrhythmia during resting ECG should not be overinterpreted as Holter examination is always necessary. Moreover, the breed distribution of the study may have influenced its results, although we did not statistically prove any breed association or dependency. Further studies are necessary to corroborate our findings.

In conclusion, our study focused on the relationship and dependency between hypothyroidism and DCM. A positive correlation between the TSH value and body weight, TSH value and left atrium size, TSH value and NTproBNP value was found in patients with preclinical DCM. An interesting finding was the difference in the incidence of arrhythmias. There were no VPC in the hypothyroid patients with DCM in contrast to the euthyroid patients with DCM where VPCs were found in 26% of them. Hypothyroid patients with DCM showed only AT. Although our study did not confirm a direct relationship between hypothyroidism and DCM as a possible cause, other correlations were discovered that have not yet been described in veterinary medicine.

Conflict of Interest

The authors declare no conflict of interest.

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