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The Role of Hypothyroidism in the Etiology and Progression of Dilated Cardiomyopathy in Doberman Pinschers

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Background: Hypothyroidism and dilated cardiomyopathy (DCM) are both common diseases in Doberman Pinschers. A possible influence of hypothyroidism on the etiology and progression of DCM is controversial.

Objectives: Evaluation of the role of hypothyroidism in etiology and progression of DCM.

Animals: A total of 175 Doberman Pinschers.

Methods: In this longitudinal prospective study, echocardiography and 24-hour ambulatory ECG recordings were performed in all dogs as screening tests for DCM. Total thyroxine (TT_4) and thyroid ultrasonography served as initial screening tests for hypothyroidism and low TT_4 values were followed up by a thyroid stimulating hormone (TSH) test or free total thyroxine (fT_4)/cTSH measurements. Additionally, a follow-up study of dogs affected by both DCM and hypothyroidism under optimal treatment for hypothyroidism was conducted.

Results: A total of 107 dogs were healthy, 45 dogs had DCM, 11 hypothyroidism, and 12 dogs had both DCM and hypothyroidism. TT_4 values as well as the thyroid volumes were equivalent in the healthy dogs and in those with DCM. Neither ventricular premature complexes nor echocardiographic parameters differed between healthy and hypothyroid dogs. Dogs with DCM had a 2.26-fold ($CI_{0.95}$ = 1.1–4.8) higher risk of also being affected by hypothyroidism. Despite optimal thyroid treatment of dogs with hypothyroidism and DCM, there was a progression of the heart disease.

Conclusions and Clinical Importance: This study did not confirm a role of hypothyroidism in the etiology or progression of DCM. Treatment of hypothyroidism did not improve the clinical outcome.

Key words: Dogs; Echocardiography; Euthyroid sick syndrome; Thyroid sonography.

Dilated cardiomyopathy (DCM) is the most common acquired cardiac disease in large and giant-breed dogs.[1,2] Certain breeds, like the Doberman Pinscher, are overrepresented.[2–4] The reported cumulative prevalence of DCM in Dobermans is 58.2%. The authors calculated a cumulative prevalence, because the prevalence differs in various age groups.[5] Because of familial clustering, an autosomal dominant inheritance is suspected regarding this breed.[5,6]

Besides a familial or genetic etiology of DCM, several other etiologies are known to cause secondary cardiomyopathies, including nutritional, inflammatory, infectious, infiltrative, ischemic, and drug- or toxin-induced myocardial diseases.[2] Furthermore, immunologic abnormalities, biochemical alterations, tachycardia-induced cardiomyopathies, and metabolic disorders can be causative.[2] One of these possible metabolic disorders is hypothyroidism, which is one of the most common endocrine disorders in dogs.[7,8] Doberman Pinschers are particularly prone to develop hypothyroidism.[9]

Thyroid hormones have positive inotropic and chronotropic effects.[7] They multiply the number of beta-adrenergic receptors and increase their affinity and the response to catecholamines.[7,10] The inotropic state of the left ventricle seems to be related to the thyroid state in experimental conditions and also in hypothyroid dogs undergoing medical treatment.[11,12] In case of hormone deficiency, reduced left ventricular systolic function, low QRS voltages, inverted T waves, weak apex beat, and sinus bradycardia are common cardiovascular abnormalities.[7,13,14] Therefore, it has been assumed that hypothyroidism might play a role in the development or progression of DCM.[10] Other studies, however, have failed to show a relationship between these 2 diseases.[4,15] No relation could be detected between hypothyroidism and DCM in Doberman Pinscher dogs.[16] A common problem encountered in veterinary practice is the euthyroid sick syndrome (ESS),

Abbreviations:

BSA	body surface area
BW	body weight
cTSH	canine thyroid stimulating hormone
DCM	dilated cardiomyopathy
DCPAH	Diagnostic Center for Population and Animal Health
ESS	euthyroid sick syndrome
FS	fractional shortening
fT_4	free total thyroxine
Holter	24-hour ambulatory ECG
LVEDV	left ventricular end-diastolic volume
LVESV	left ventricular end-systolic volume
LV	left ventricle
RR	relative risk
RTV	relative thyroid volume
SMOD	Simpson method of disc
T_4AA	autoantibodies against TT_4
TgAA	thyroglobulin autoantibodies
TS	thyroid sonography
TT_4	total thyroxine
TV	total thyroid volume
VPCs	ventricular premature complexes

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also known as sick euthyroid syndrome, which refers to a state, where concurrent nonthyroidal illness causes suppression of serum concentrations of circulating thyroid hormone without true pathology of the thyroid gland. Decreased concentrations of total thyroxine (TT_4) and to a lesser degree free total thyroxine (fT_4) in ESS can be misleading and might result in an erroneous diagnosis of hypothyroidism.[17] ESS has been described to occur with various cardiac diseases,[17] for example, in Doberman Pinschers with CHF.[16] Thyroid sonography is an effective tool to discriminate between hypothyroid and euthyroid sick dogs.[18]

Because there are still many controversial discussions as well as different opinions regarding DCM and hypothyroidism, the diagnosis of DCM might be delayed and some dogs with DCM might receive only treatment for hypothyroidism, but not for their cardiac disease. Some owners or veterinarians are reluctant to give cardiac drugs, because they think that treatment for hypothyroidism would be sufficient. These dogs might have potentially life-threatening arrhythmias or a morphologically abnormal heart. A treatment of these changes would not only prolong their lives but could also increase their quality of life.[19]

Therefore, the aim of this study was to examine if hypothyroidism has a modifying affect on the onset and clinical course of DCM in a large cohort of Doberman Pinschers. Furthermore, the therapeutic benefits of hypothyroidism treatment on the clinical outcome and the presence of ESS in different stages of DCM were evaluated.

Material and Methods

Study Design and Animals

This study was a prospective clinical trial from September 2011 to February 2013. Doberman Pinschers were recruited according to the inclusion and exclusion criteria listed below. The animals were all client-owned dogs. The study fulfilled the general German guidelines for prospective studies with informed owners' consent. The study consisted of 2 parts: (1) Assessment of DCM and of hypothyroidism in Doberman Pinschers. (2) Follow-up study of dogs affected by both DCM and hypothyroidism, under optimal treatment for hypothyroidism.

Inclusion Criteria. The study included all Doberman Pinschers, which were presented to the department of cardiology of the Clinic of Small Animal Medicine, LMU University of Munich, between September 2011 and February 2013. Main reasons for the presentation of the dogs at the clinic were DCM screening purposes or regular recheck visits, if they had been previously diagnosed with DCM.

Exclusion Criteria. Dogs were excluded, if they had a severe systemic (eg, acute kidney failure, sepsis) or chronic disease (eg, diabetes mellitus, chronic kidney failure) of any kind other than hypothyroidism or DCM. In nonthyroidal illness, the TT_4 concentration tends to decrease and this complicates the diagnosis of hypothyroidism.[7,20] Furthermore, dogs participating in this study were not allowed to receive corticosteroids, nonsteroidal anti-inflammatory drugs, phenobarbital, or sulfonamides during the whole study duration, because these drugs might influence the thyroid gland.[7,21,22] Besides DCM, all other congenital or acquired heart diseases led to study exclusion.

Examinations. A detailed history was acquired and all dogs were subject to a clinical examination.

Cardiac Examination. In all dogs, an in-house ECG, a 24-hour ambulatory ECG (Holter), as well as a complete echocardiographic study, were performed. The ECG[a] was recorded in right lateral recumbency according to standard technique. The Holter recordings were analyzed with one of two commercial software programs.[b,c] Manual adjustments and accuracy verification of the arrhythmias recognized by the software were performed. The presence and number of ventricular premature complexes (VPCs) were recorded.

The echocardiography was performed in right and left lateral recumbency in nonsedated dogs. A high frame rate ultrasound system[d] with a 2.0/4.3 MHz transducer was used. Left ventricular volume was measured by Simpson's method of discs (SMOD) in the right parasternal long-axis view and additionally in the left parasternal apical 4-chamber view. The end-diastolic and end-systolic LV volumes (LVEDV, LVESV) were indexed to body surface area (BSA).[23] For determination of the DCM status and the statistical analysis only the larger value of both views was used. Color-Doppler was used to search for congenital or acquired cardiac diseases. Pulsed-wave Doppler was used to measure the velocities over the aortic and the pulmonic valves. For inclusion these velocities had to be <2.2 m/s. The follow-up interval for the cardiac status was dependent on the observed findings. Healthy dogs were rechecked once a year, the dogs with congestive heart failure every 3–6 months, the others dependent on their needs. The complete cardiac examination, inclusive echocardiography and Holter were repeated.

Determination of the DCM Status. Dogs were classified as having DCM, if LVEDV/BSA was >95 mL/m^2 or LVESV/BSA was >55 mL/m^2.[23] More than 100 VPCs in 24 hours in the Holter-ECG were indicative of DCM.[24] Dogs that had between 50 and 100 VPCs/24 hours and a normal echocardiographic examination were considered equivocal and were not included in the statistical analysis.[23,24]

Cardiac Treatment. All dogs with systolic dysfunction received Pimobendan.[e] Depending on Holter results and the individual disease progression, dogs received further medication, either one drug or a combination of the following: Ramipril,[f] Sotalol Hydrochloride,[g] Amiodarone Hydrochloride,[h] Mexiletine.[i] In case of decompensation (presence of pulmonary edema, pleural effusion, or ascites), Fursosemide[j] was added.

Investigation of Hypothyroidism. As a first screening test, a thyroid ultrasound and TT_4 measurements were performed. Plasma TT_4 concentrations were measured with a chemiluminescent enzyme immunoassay. The reference range was 12.9–51.5 nmol/L (1.0–4.0 μg/dL).

The thyroid sonography was performed by an experienced investigator (SR) in a quiet room, with unsedated dogs in a sitting position. One of two high frame rate ultrasound systems (My Lab Twice and My Lab 40[k]) with a 7.5–13 MHz linear array probe[l] was used. Thyroid glands were scanned in longitudinal and transversal planes. Size, echogenicity, and homogeneity of the thyroid lobes were examined.[7] The thyroid lobe volume was calculated and related to metabolic weight ($BW^{0.75}$). A relative thyroid volume (RV) <0.05 $mL/kg^{0.75}$ was indicative of hypothyroidism.[18]

Dogs with a TT_4 below the reference range or an abnormal thyroid ultrasound received one or several additional thyroid tests. In agreement with the owners and if the dogs were not yet under treatment for hypothyroidism, a TSH-stimulating test was performed.[7] For this test, TT_4 was measured before and 6 hours after the administration of 150 μg/dog recombinant human TSH (thyrotropin alpha).[m] ,[25] The results of the TSH-stimulation tests were interpreted according to criteria established in

previously published studies.[25,26] Briefly, a poststimulation TT_4 concentration of >2.5 μg/dL and values being at least 1.5 times the basal TT_4 concentration were considered a normal euthyroid test result. TSH-stimulation test results with post-TSH TT_4 concentrations between 1.6 and 2.5 μg/dL and a post-TSH TT_4 concentration of >1.5 times basal TT_4 in dogs without clinical signs of hypothyroidism were also considered normal in this study. Dogs with post-TSH TT_4 concentrations of <1.6 μg/dL and <1.5 times the basal TT_4 were classified as hypothyroid. Additionally, all blood samples of dogs with low or high TT_4, altered thyroid sonography, or both were sent to the Diagnostic Center for Population and Animal Health (DCPAH) at Michigan State University, to run a detailed canine thyroid diagnostic profile,[n] including fT_4 by equilibrium dialysis, canine TSH (cTSH), thyroglobulin autoantibodies (TgAA), and autoantibodies directed against TT_4 (T_4AA). Dogs with a low TT_4, but a normal thyroid profile as well as a normal thyroid ultrasound, were classified as euthyroid.

Determination of the Thyroid Status. Dogs were classified as hypothyroid, (1) if they had a positive TSH-stimulation test; (2) if they had a TT_4 value below the reference range and a cTSH higher than the reference range; or (3) if they were presented under treatment, the relative thyroid volume had to be <0.05 $mL/kg^{0.75}$ and they had to have a reduced echogenicity and homogeneity of the thyroid gland.[18,27] Ongoing treatment for hypothyroidism was not stopped to confirm the diagnosis of hypothyroidism, if it was likely that these dogs suffer from hypothyroidism (relative thyroid volume <0.5 $mL/kg^{0.75}$), because it was considered to be unethical. Dobermans were classified as euthyroid if (1) TT_4 was within the reference range and the thyroid sonography showed no abnormalities; or if (2) TT_4 and the thyroid profile were normal and no evidence of clinical signs of hypothyroidism, despite an abnormal relative thyroid volume, but normal echogenicity and homogeneity.

The thyroid status was declared questionable, if the value of TT_4 was low or high and there was no confirmatory test possible. Dogs were classified as euthyroid sick, if they had a low TT_4 only and DCM. The rest of the thyroid diagnostics were normal in this case. The term ESS was also used in previously published studies to describe a low TT_4 in combination with a nonthyroidal illness.[18,20,28] In Figure 1, the determination of the thyroid status is displayed graphically.

Treatment of Hypothyroidism. Once hypothyroidism was confirmed, the dogs received a starting dose of 0.02 mg/kg Levothyroxine[o] 2 times a day. The TT_4 was rechecked 4 weeks after starting treatment—6 hours after tablet administration. If

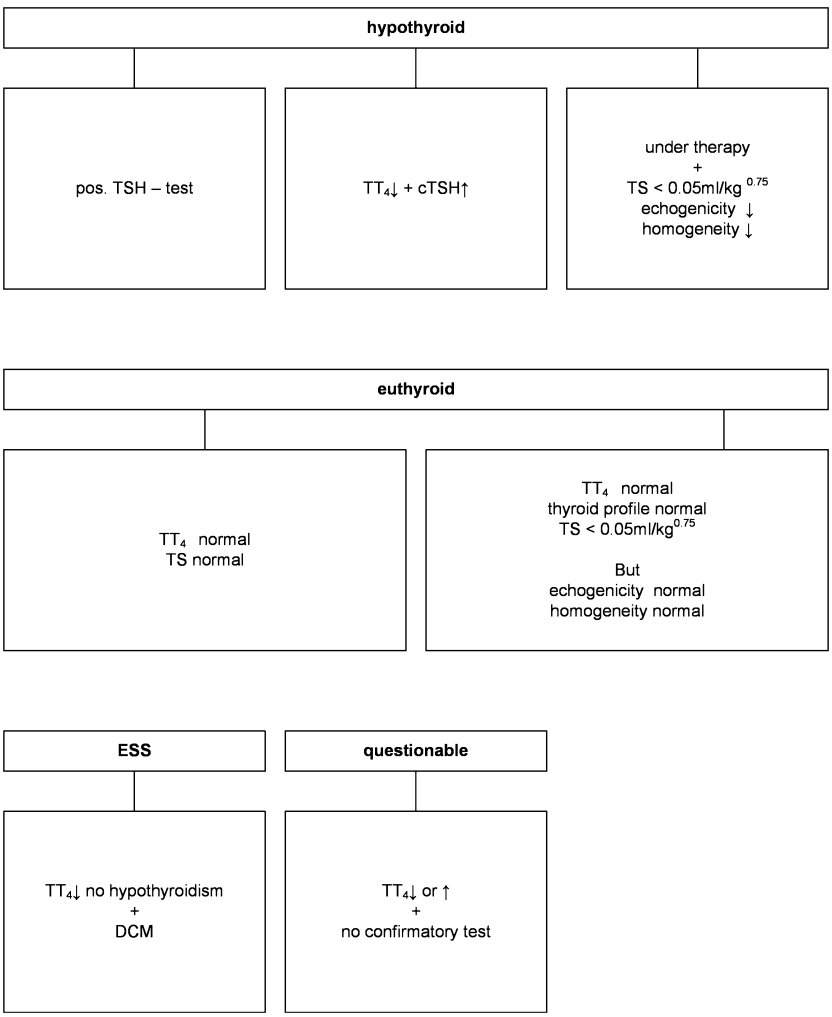

Fig 1. Flowchart to demonstrate the determination of the thyroid status. Pos. TSH test, positive test result in the thyroid stimulating hormone test; TT_4, total thyroxine; TS, thyroid sonography; cTSH, canine TSH; DCM, dilated cardiomyopathy; ESS, euthyroid sick syndrome.

necessary, the treatment was adjusted. Treatment was considered optimal, if the value of TT_4 was in the upper part or slightly above the reference range.[29] If dogs were in congestive heart failure (CHF), the starting dose was reduced to 0.01 mg/kg Levothyroxine 2 times a day, because of potential worsening of heart failure by restoring the euthyroid state.[30]

Group Classification and Statistical Analysis

Two commercially available software programs were used for statistical analysis.[p,q] According to the initial examination of each dog, dogs were assigned to one of the four following groups: (1) healthy, (2) DCM, (3) hypothyroidism, or (4) DCM + hypothyroidism. These 4 groups were applied for all further investigations. Relative frequencies, as well as relative risks (RRs) and 95% confidence intervals, were calculated.[31] The RR is the ratio of the probability of an event occurring in an exposed group to the probability of the event occurring in a comparison, nonexposed group. It is used to compare the risk of developing a disease.[31,32] To compare the prevalence of hypothyroidism in the healthy versus the DCM group, we used the chi-square test.[31] The influence of age and the SMOD results were examined using a 1-way ANOVA test and posthoc Bonferroni correction. Student's *t*-test for independent samples was used to analyze the influence of weight and to investigate the results of the thyroid sonography. The influence of VPCs in the different groups was evaluated with the Kruskal-Wallis test and a posthoc Mann-Whitney *U*-test. To test equivalence, the equivalence test for averages by Schneider was used.[33] Furthermore, the effect sizes and their 95% confidence intervals of age, TT_4, thyroid sonography, and SMOD values were determined. An effect size (Cohen's *d*) >0.80 is indicative for a great influence of the disease status on the examined parameter.[34]

As a second part of the study, the course of the heart disease of those dogs affected by both DCM and hypothyroidism was evaluated. A paired *t*-test was used to compare SMOD values before and under hypothyroidism treatment; additionally a Wilcoxon test was used to examine the number of VPCs between the first and the second examination. A *P*-value <.05 was considered statistically significant.

Results

Dogs

A total of 184 Doberman Pinschers were examined during the study period; 175 Doberman Pinschers with a median body weight of 35.0 kg (range 22.6–49.8 kg) and a median age of 6.00 years (range 1–13 years) fulfilled the inclusion and exclusion criteria. Eight dogs were excluded because their cardiac status was ambiguous. They were neither definitely ill nor healthy. One dog was excluded because of a TT_4 above the reference range and no follow-up. Ninety-seven (55.1%) of the 175 dogs were female and 78 (44.9%) male. At the time of study inclusion, 118/175 (67.4%; $CI_{0.95}$ = 60.4–74.3%) of the dogs had a normal cardiac examination including echocardiography and Holter, 57 (32.6%) dogs were diagnosed with DCM. Of the dogs with DCM, 17 (9.7%) dogs had only VPCs, 20 (11.4%) dogs showed only echocardiographic changes, and 12 (6.9%) patients had both VPCs and echocardiographic changes. Eight (4.6%) dogs were in CHF. Six of the CHF dogs had VPCs and echocardiographic changes, the remaining 2 dogs only had echocardiographic changes. Hypothyroidism was diagnosed in 23 (13.1%) Doberman Pinschers. The results of the thyroid classification and how the diagnosis was made are shown in Figure 2. According to a combined thyroid and cardiac status, the dogs were assigned to one of the 4 groups as mentioned earlier: (1) healthy (n = 107, 61.1%), (2) DCM only (n = 45, 25.7%), (3) hypothyroidism only (n = 11, 6.3%), and (4) DCM + hypothyroidism (n = 12, 6.9%). Table 1 shows the mean, or the median and the range of the examined cardiac and thyroid parameters in the 4 groups. Table 2 shows the same parameters, but split up by the DCM status for the DCM + hypothyroidism and the DCM only group. The prevalence of hypothyroidism was higher in the DCM group (12/57, 21.1%) compared with the healthy group (11/118, 9.3%) in this study (P = .031). Seven dogs in this study had DCM and a low TT4 and were classified as ESS.

Relative Risk

A Doberman Pinscher, diagnosed with hypothyroidism, has a 1.76-fold ($CI_{0.95}$ = 1.1–3.0) increased risk to develop DCM. Furthermore, a dog suffering from DCM has a 2.26-fold ($CI_{0.95}$ = 1.1–4.8) increased risk to develop hypothyroidism.

Group Comparisons

Age and Body Weight. Healthy dogs (median: 5.00 years) were significantly (P < .001) younger than dogs diagnosed with DCM (median: 7.00 years) or with DCM + hypothyroidism (median: 9.00 years). Hypothyroid dogs had a median age of 6.00 years and were significantly (P = .036) younger than the DCM + hypothyroidism group. The hypothyroid dogs (mean weight: 38.35 kg) were 9% heavier (P = .027) than the healthy dogs (mean weight: 34.54 kg). Dogs belonging to the DCM + hypothyroidism group had a mean body weight of 37.18 kg, whereas dogs in the DCM only group had a mean weight of 36.62 kg—not statistically significant (P = .770).

Cardiac Variables. Regarding the number of VPCs/24 hours, there was neither a difference between healthy (median: 1.00) and hypothyroid dogs (median: 1.00) (P = .514), nor a statistically significant (P = .394) difference between dogs with DCM (median: 249.00) and dogs with both, DCM and hypothyroidism (median: 155.00). Dogs with DCM or both diseases had significantly more VPCs than healthy or hypothyroid dogs (P < .001).

There was no significant difference of LVEDV/BSA and LVESV/BSA between the healthy and the hypothyroid group (P = 1.00). However, both groups had significantly smaller LVEDV/BSA and LVESV/BSA SMOD values compared with both, the DCM group and the DCM + hypothyroidism group (for all P < .001, Table 1). There was no significant difference in heart size between the DCM and the DCM + hypothyroidism

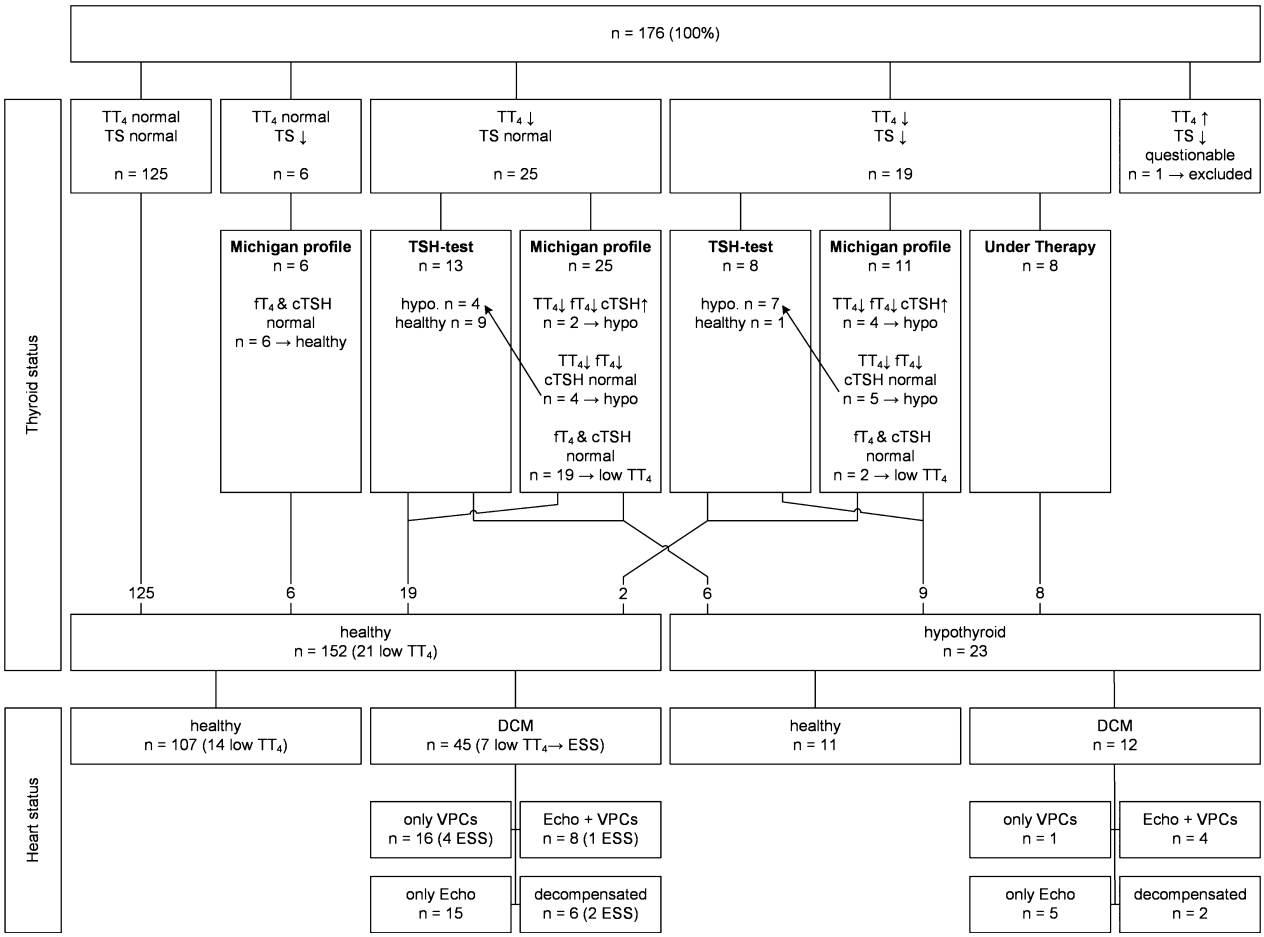

Fig 2. Flowchart to show the results of the classification of the thyroid status. TT_4, total thyroxine; TS, thyroid sonography; TSH test, thyroid stimulating hormone test; fT_4, free T_4; cTSH, canine TSH; hypo, hypothyroid; n, number of dogs; DCM, dilated cardiomyopathy; VPCs, ventricular premature complexes; Only ECHO, only echocardiographic changes; ESS, euthyroid sick syndrome.

Table 1. Mean or median and range of total thyroxine (TT_4), relative thyroid volume (RV), the number of Holter ventricular premature complexes (VPCs), and Simpson method of disc left ventricular end-systolic and end-diastolic volume (LVEDV, LVESV) indexed to body surface area (BSA) of the 175 study participating dogs.

Variables	Healthy (n = 107)	DCM Only (n = 45)	Hypothyroidism (n = 11)	DCM + Hypothyroidism (n = 12)
TT_4 (nmol/L), mean (range)	19.54 (9.01–45.04)	19.59 (9.01–34.75)	10.06 (9.01–11.58)	9.76 (9.01–11.58)
RV ($mL/kg^{0.75}$), mean (range)	0.08 (0.04–0.18)	0.07 (0.05–0.13)	0.05 (0.03–0.10)	0.05 (0.02–0.10)
Holter VPCs, median (range)	1 (0–49)	249 (0–16,512)	1 (0–5)	155 (0–53,815)
LVEDV/BSA (mL/m^2), mean (range)	79.85 (55.50–94.90)	105.08 (68.20–207.90)	76.75 (69.90–89.20)	119.31 (78.31–191.10)
LVESV/BSA (mL/m^2), mean (range)	40.60 (17.20–54.80)	64.96 (33.20–154.00)	35.77 (25.10–50.40)	75.73 (35.03–164.10)

group assessed by LVEDV/BSA ($P = .130$) and LVESV/BSA ($P = .294$). With respect to LVEDV/BSA statistical equivalence between these groups was demonstrated ($P = .050$). The effect sizes, showing the influence of hypothyroidism on SMOD values, were low ($d = 0.34$ LVEDV/BSA ($CI_{0.95} = -0.28$ to 0.96), $d = 0.63$ LVESV/BSA ($CI_{0.95} = 0.00$–1.25) healthy versus hypothyroid dogs, $d = 0.48$ LVEDV/BSA ($CI_{0.95} = -0.17$ to 1.1), $d = 0.39$ LVESV/BSA ($CI_{0.95} = -0.25$ to 1.03) DCM versus DCM + hypothyroidism group). Therefore, these low effect sizes indicate no relevant influence of hypothyroidism on the SMOD values.

Thyroid Variables. The TT_4 measurements of healthy dogs and dogs suffering from DCM were equivalent ($P = .050$). The effect sizes of the hypothyroid group versus DCM + hypothyroidism group ($d = 0.28$ [$CI_{0.95} = -0.55$ to 1.09]) and the healthy versus the DCM group ($d = 0.010$ [$CI_{0.95} = -0.34$ to 0.36]) were very low and consequently indicate no influence of DCM on TT_4 values. A low TT_4 value

Table 2. Mean or median and range of total thyroxine (TT_4), relative thyroid volume (RV), the number of Holter ventricular premature complexes (VPCs), and Simpson method of disc left ventricular end-systolic and end-diastolic volume (LVEDV, LVESV) indexed to body surface area (BSA) of DCM only (DCM, highlighted) and the DCM + hypothyroidism (DCM + hypo unhighlighted) group divided according to their dilated cardiomyopathy (DCM) status. ECHO only: only echocardiographic changes.

	VPCs Only		ECHO Only		VPCs + ECHO		Decompensated	
DCM Category	DCM Only (n = 16)	DCM + Hypo (n = 1)	DCM Only (n = 15)	DCM + Hypo (n = 5)	DCM Only (n = 8)	DCM + Hypo (n = 4)	DCM Only (n = 6)	DCM + Hypo (n = 2)
TT_4 (nmol/L), mean (range)	17.45 (9.01–30.89)	10.30 (10.30)	19.39 (12.87–27.03)	9.78 (9.01–11.58)	23.17 (10.30–34.75)	9.97 (9.01–11.58)	21.02 (9.01–32.17)	9.01 (9.01)
RV ($mL/kg^{0.75}$), mean (range)	0.07 (0.05–0.13)	0.07 (0.07)	0.07 (0.05–0.11)	0.05 (0.03–0.07)	0.07 (0.05–0.10)	0.04 (0.02–0.05)	0.09 (0.07–0.12)	0.07 (0.04–0.10)
Holter VPCs, median (range)	1,413 (114–10,000)	231 (231)	4 (0–27)	1 (0–6)	573 (345–16,512)	407 (102–53,815)	241 (64–3,010)	2,499 (733–4,265)
LVEDV (mL/m^2), mean (range)	81.26 (68.20–92.90)	78.31 (78.31)	108.73 (96.90–149.50)	105.70 (86.00–142.30)	120.98 (96.20–207.90)	111.15 (95.70–124.60)	138.32 (99.10–194.40)	190.15 (189.20–191.10)
LVESV (mL/m^2), mean (range)	43.83 (33.20–54.70)	35.03 (35.03)	66.65 (53.90–97.20)	65.32 (55.50–89.90)	76.83 (57.10–154.00)	69.27 (59.56–88.80)	101.27 (66.30–138.40)	135.05 (106.00–164.10)

was documented in 13.1% of the healthy dogs and in 15.6% of the dogs in the DCM group.

Total and relative thyroid volume (TV, RV) of dogs suffering from DCM and healthy dogs was statistically equivalent ($P = .050$). Hypothyroid dogs had a significant smaller TV ($P = .0021$) and RV ($P < .001$) than healthy dogs or those affected with DCM (TV: $P = .0080$, RV: $P < .001$). Furthermore, dogs suffering from both diseases showed likewise a significant difference compared with healthy ($P < .001$) and DCM dogs ($P < .001$). Again, the effect sizes of the hypothyroid group versus DCM + hypothyroidism group (d = 0.18 [$CI_{0.95} = -0.65$ to 0.99]) and the healthy versus the DCM group ($d = 0.16$ [$CI_{0.95} = -0.19$ to 0.51]) were low and indicate no relevant influence of DCM on the thyroid sonography measurements.

Follow-up Examinations. Eight of the twelve dogs included in the DCM + hypothyroidism group were presented for a recheck examination (mean 4 months, range 3–6 months). The second investigation was carried out with optimal adjusted thyroid treatment (as described in Material and Methods section). Three dogs were newly diagnosed with hypothyroidism; 5 dogs had already been diagnosed with hypothyroidism and treatment with Levothyroxine had been started already. The remaining 4 dogs could not be rechecked, because they died before the follow-up appointment. Two dogs died because of congestive heart failure, one because of sudden death and one dog was lost on follow-up. The dogs showed significantly more VPCs at the second examination ($P = .018$). Furthermore, the SMOD values progressed significantly at the recheck visit, as indicated by an increase of LVEDV/BSA ($P = .010$) and LVESV/BSA ($P = .021$) compared to the values of the first visit.

Discussion

Hypothyroidism and DCM are both common diseases in Doberman Pinschers.[5,12,35–37] Although it appears that there might be a link between both diseases according to the results of this study, which showed that Doberman Pinschers with DCM have a 2.26-fold increased risk to develop hypothyroidism, hypothyroidism does not seem to play a role in the etiology or progression of DCM in this breed. This statement is supported by several findings of the present study, such as that there was no difference in cardiac size or number of VPCs comparing the healthy group and the hypothyroid group and also by the ongoing deterioration of the SMOD values and the number of VPCs despite optimal thyroid treatment in dogs affected by both DCM and hypothyroidism.

The role of hypothyroidism regarding the etiology of DCM is discussed controversially in the literature. Several authors state that hypothyroidism leads to impaired left ventricular function in dogs.[7,13,14] The same finding is described in the human literature.[38–41] However, this systolic dysfunction is rarely clinically important.[30,36,41] But in the veterinary[14,42–44] as well as

in the human literature,[39,45–47] some authors suspected that hypothyroidism could exacerbate a preexisting myocardial dysfunction and even lead to heart failure. Because of this, hypothyroidism was mentioned to possibly cause DCM in dogs[10,48] and in humans.[49–51] Other veterinary studies, however, could not identify a relationship between hypothyroidism and cardiomyopathy with or without congestive heart failure, including a study in Doberman Pinschers.[15,16,52,53] In the present study, we did not find a significant difference in cardiac size between the healthy and the hypothyroid group and there was also no difference between the DCM and DCM + hypothyroidism group. Also, whereas in a few cases an improvement of cardiac function has been reported under thyroid treatment,[42–44] no improvement of the cardiac variables or at least a disease standstill was observed in the dogs of the DCM + hypothyroidism group in the follow-up study under optimal adjusted thyroid treatment. These results speak clearly against a role of hypothyroidism in the etiology or progression of DCM in Doberman Pinschers.

A feature of DCM in Doberman Pinschers is the common presence of VPCs and ventricular tachyarrhythmias.[24] In humans, malignant ventricular arrhythmias are reported to occur in some patients with hypothyroidism.[54,55] However, these ventricular arrhythmias seem to disappear with thyroid treatment in humans.[56,57] Assuming hypothyroidism would cause VPCs in dogs and potentially by doing that a secondary tachycardia-induced DCM, one would expect to find more VPCs in dogs with only hypothyroidism. However, in the present study, there was neither a significant difference regarding the number of VPCs between the healthy and the hypothyroid nor the DCM and the DCM + hypothyroidism group. Additionally, in the follow-up study, the VPCs did not disappear under thyroid treatment; they even became more severe. Therefore, according to the results of our study, VPCs in Dobermans are related to DCM and not to hypothyroidism.

The published all-breed prevalence of hypothyroidism is between 0.2 and 0.8%.[9,10,12] Doberman Pinschers have an increased risk to be additionally affected by hypothyroidism[12,35,36] and this is in agreement with the results of the current study, in which the relative frequency of hypothyroidism in Doberman Pinschers was 13.1%. Whereas the incidence of hypothyroidism in the DCM group (21.1%) was higher than in the healthy group (9.2%) in the present study, one study reported that the prevalence of hypothyroidism in the DCM group was not higher compared with the group with noncardiac diseases.[16] An explanation for this discrepancy might be the significantly lower age of the healthy group in the current study, as the average age at diagnosis of hypothyroidism is 7 years[9,10,12] and DCM in Doberman Pinschers is also more frequently diagnosed in older dogs.[2,5] Therefore, it is not surprising that hypothyroidism was more often diagnosed in the DCM group compared with the healthy group.

Whereas hypothyroidism did not play a role in the etiology or progression of DCM in this study, we found that the RR to be additionally affected by DCM was increased in hypothyroid dogs. Dogs suffering from DCM even have a 2.26-fold higher risk to be also affected by hypothyroidism. One possible explanation could be that Doberman Pinschers have a breed predisposition for both diseases, independent from each other. Thus, there might be a more frequent joint occurrence of the two diseases, without having a causal relationship.[10] This hypothesis is strengthened by the fact that both diseases tend to affect older dogs and the dogs in the healthy group in this study were significantly younger. Another possibility might be a common pathway in the pathogenesis of both diseases as, for example, an immune-mediated origin. Immunologic processes might play a role in the pathogenesis of DCM,[1,2,58,59] as well as in the development of hypothyroidism,[7,60] but further studies are needed to confirm this hypothesis.

Euthyroid sick syndrome is a condition in dogs, where concurrent nonthyroidal illness causes suppression of serum concentrations of circulating thyroid hormone without true pathology of the thyroid gland. Decreased concentrations of TT_4, and to a lesser degree fT_4, with ESS can be misleading and result in an erroneous diagnosis of hypothyroidism.[17] According to the results of our study, ESS appears to be an uncommon finding in Doberman Pinschers with DCM. Low TT_4 values were detected in 14 dogs in the control group and 7 dogs in the DCM group, in which the confirmatory thyroid function tests ruled out hypothyroidism. Therefore, 7 dogs would fulfill the criterion for ESS, but it is questionable whether this represents real ESS because of DCM or low TT_4 values attributable to other reasons, like in the healthy group. Possible other origins for low TT_4 values are normal fluctuation,[61] extreme exercise,[20] and inadequate caloric intake.[62] Speaking against ESS is the fact that the TT_4 values as well as the percentages of low TT_4 dogs in the healthy and DCM group are similar (13.1%/15.6%). Additionally one would suspect to find ESS more often in advanced DCM stages[17]; however, this was not the case, as the 7 dogs are distributed to 3 of the 4 possible DCM subgroups. Because the thyroid sonography is an effective tool to discriminate between hypothyroid and euthyroid sick,[18] the thyroid gland of each dog was scanned. The TV and RV did neither differ between the healthy group and DCM group nor between the hypothyroid group and the DCM + hypothyroidism group. Consequently, DCM does not have any influence on thyroid sonography. If it is assumed that hypothyroidism and DCM influence each other, there should have been more abnormal thyroid sonographies in the DCM group.

A limitation of the study is that all dogs suffering from cardiac disease received cardiac treatment depending on their needs. Therefore, especially in the DCM + hypothyroidism group, almost every dog received a different treatment. But this cardiac treat-

ment was not changed between the first and the recheck examination. However, the influence of cardiac treatment on the results cannot be ruled out completely. Another important limitation is the low numbers of dogs in the follow-up study; larger studies with a control group should be conducted. Because of the low number in the DCM + hypothyroidism group, some confidence intervals of the effect sizes were very wide. However, because all values of the effect sizes are far away from the limit $d > 0.80$, which indicates a great influence of the disease status on the examined parameters, they are still convincing.[34]

In conclusion, this study shows that both hypothyroidism and DCM are common diseases in Doberman Pinschers, but there is no influence of hypothyroidism on the etiology and progression of DCM. Also, the occurrence of an ESS is very uncommon in Doberman Pinschers suffering from DCM with or without clinical signs.

Footnotes

[a] Schiller Cardiovit AT-10; Schiller Medizintechnik Gmbh, Germany
[b] Custo tera; Arcon Systems GmbH, Starnberg, Germany
[c] Amedtech ECGpro Holter software, EP 810 digital Recorder; Medizintechnik Aue GmbH, Aue, Germany
[d] Vivid 7 dimension; General Electric Medial System, Waukesha, WI
[e] Vetmedin®; Boehringer Ingelheim, Ingelheim, Germany
[f] Vasotop®; MSD Animal Health GmbH, Unterschleißheim, Germany
[g] Sotalol-ratiopharm®; Ratiopharm GmbH, Ulm, Germany
[h] Amiodaron 200®; 1 A Pharma GmbH, Oberhaching, Germany
[i] Ritalmex 200®; Valeant Pharmaceuticals International Inc. Laval, QC
[j] Dimazon; MSD Animal Health GmbH, Unterschleißheim, Germany
[k] Esaote_Piemedical, Köln, Germany
[l] Linearray type LA523; Esaote_Piemedical
[m] Thyrogen®, genzyme therapeutics; Genzyme corporation, Cambridge, Mass, UK
[n] Premium canine thyroid profile, Order Code 20011
[o] Forthyron®; Eurovet Animal Health B.V., Bladel, Netherlands
[p] PASW Statistics 18 SPSS for Windows, Version 13.0, SPSS Inc., Chicago, IL
[q] MedCalc, Version 8.1, Mariakerke, Belgium

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Off-label Antimicrobial Declaration: The authors declare no off-label use of antimicrobials.

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