Evaluation of a Feline-Optimized TSH Assay in Cats With Hyperthyroidism and With Non-Thyroidal Illness

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Thesis submitted to the Faculty of the Virginia Polytechnic Institute and State University in partial fulfillment of the requirements for the degree of

Master of Science
In
Biomedical and Veterinary Sciences

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July 26, 2024

Blacksburg, Virginia

Keywords: feline hyperthyroidism, non-thyroidal illness syndrome, thyrotropin, thyroid stimulating hormone, bulk acoustic wave technology, TSH assay

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ABSTRACT (academic)

About 10% of hyperthyroid cats have a normal total T4 (TT4), requiring further testing to make the diagnosis. Thyroid stimulating hormone (TSH) is measured using the “canine” assay (TSH-CLIA, Immulite 2000 by Siemens) as the only assay currently available. However, this assay cannot differentiate between subnormal and low-normal TSH concentrations in cats due to poor specificity (70-85%). A novel feline-optimized TSH assay (TSH-BAW, Truforma by Zomedica) was recently developed. It allows differentiation between euthyroid and hyperthyroid cats. However, the effect of non-thyroidal illness (NTI) on TSH-BAW has not been evaluated. Our objectives included the comparison of serum TSH concentration using both the TSH-CLIA and TSH-BAW assays among hyperthyroid cats, cats with NTI, and healthy cats, and the evaluation of the sensitivity and specificity of the TSH-BAW for diagnosis of FHT. This prospective cross-sectional study was performed on 102 client-owned cats, including 37 hyperthyroid, 33 healthy, and 32 NTI cats. The following thyroid hormones were measured in all cats: TT4, TSH with both assays (Immulite 2000 and Truforma). Hyperthyroidism was confirmed by thyroid scintigraphy. Euthyroidism was confirmed by repeating TT4 measurement at least three months after enrollment (if available) to rule out subclinical hyperthyroidism. Cats with NTI were further divided based on the severity of their illness. Serum TSH was compared among groups using Kruskal-Wallis followed by Dunn’s procedure, and compared among NTI severity scores using the Fisher’s Exact test. Significance was set at P <0.05. The sensitivity and specificity of TSH-BAW for detecting hyperthyroidism are 78% (62-90%) and 97% (84-100%), respectively. The median TSH is significantly different between hyperthyroid cats and healthy and NTI cats with both assays (P<0.01). The TSH was not different between the latter euthyroid groups (P=0.87 and P=0.29). Eight (21.6%) hyperthyroid cats have a normal TSH-BAW but undetectable TSH-CLIA. Twelve (4 healthy, 8 NTI) euthyroid cats (18.5%) have an undetectable TSH-CLIA with only two (1 healthy, 1 NTI) (3%) having an undetectable TSH-BAW. The proportion of cats with a suppressed TSH is higher with severe illnesses with the TSH-CLIA only. In conclusion, the TSH-BAW has a high specificity, identifies normal TSH in healthy cats more often, and appears to not be affected by NTI. It can be a useful tool for the diagnosis of feline hyperthyroidism. However, a low-normal TSH cannot be used to rule out hyperthyroidism.

Evaluation of a Feline-Optimized TSH Assay in Cats With Hyperthyroidism and With Non-Thyroidal Illness

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ABSTRACT (general)

Hyperthyroidism leads to elevation of the thyroid hormone total T4 (TT4). About 10% of hyperthyroid cats have a normal TT4, requiring further testing to make the diagnosis. Another thyroid hormone, thyroid stimulating hormone (TSH), could be used like it is with people. In feline medicine, it is measured using the “canine” assay (TSH-CLIA, Immulite 2000 by Siemens) as the only assay currently available. However, this assay cannot differentiate between subnormal and low-normal TSH concentrations in cats due to poor specificity (70-85%). A novel feline-optimized TSH assay (TSH-BAW, Truforma by Zomedica) was recently developed. It allows differentiation between euthyroid and hyperthyroid cats. However, the effect of non-thyroidal illness (NTI) on TSH-BAW has not been evaluated. Our objectives included the comparison of serum TSH concentration using both the TSH-CLIA and TSH-BAW assays among hyperthyroid cats, cats with NTI, and healthy cats, and the evaluation of the sensitivity and specificity of the TSH-BAW for diagnosis of FHT. The study was performed on 102 client-owned cats, including 37 hyperthyroid, 33 healthy, and 32 NTI cats. The following thyroid hormones were measured in all cats: TT4, TSH with both assays (Immulite 2000 and Truforma). Cats with NTI were further divided based on the severity of their illness. Serum TSH was compared among groups using Kruskal-Wallis followed by Dunn’s procedure, and compared among NTI severity scores using the Fisher’s Exact test. Significance was set at $P < 0.05$. The sensitivity and specificity of TSH-BAW are 78% and 97%, respectively. The median TSH is significantly different between hyperthyroid cats and healthy and NTI cats with both assays. The euthyroid cats (healthy and NTI cats) were not different. Eight (21.6%) hyperthyroid cats have a normal TSH-BAW (not normal in the face of hyperthyroidism) but undetectable TSH-CLIA. The proportion of euthyroid cats with a suppressed TSH (not normal in the face of euthyroidism) is higher with the TSH-CLIA compared to the TSH-BAW. Only with the TSH-CLIA, the proportion of NTI cats with a suppressed TSH is higher than healthy cats, and is higher with severe illnesses. In conclusion, the TSH-BAW has a high specificity, identifies normal TSH in healthy cats more often, and appears to not be affected by NTI. It can be a useful tool for the diagnosis of feline hyperthyroidism. However, a low-normal TSH cannot be used to rule out hyperthyroidism.

ACKNOWLEDGMENTS

This project was made possible with the help of several individuals. I would like to acknowledge my committee members for their amazing assistance throughout the project. In particular, I would like to recognize my Masters and Residency advisors, Drs. Stefanie DeMonaco and Ashley Wilkinson, for their help and support throughout the last 3 years. I could not have undertaken this journey without their patience, caring and dedication.

Additionally, I would like to thank Dr. Stephen Were for his aid with statistical analysis of our data. Thanks should also go to Zomedica for funding our project.

I am also grateful to my resident mates for their constant help and moral support. This residency would not have been the same without them.

Lastly, I would be remiss in not mentioning my friends and family, including my fur babies Sasha and Black Jack. Their reassuring presence was often required to keep me motivated and focused.

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	Hyperthyroid cats *(n = 37)*	**Euthyroid healthy cats *(n = 32)***	**Euthyroid cats with NTI *(n = 33)***	*P* - value
TT4	169.1[a] (140.7-197.5)	31.8[b] (29.5-34.1)	20.2[b] (16.6-23.8)	a/b: **<0.001** b/b: 0.66
TSH-CLIA	0.03[a] (0.03-0.03)	0.08[1] (0.06-0.1)	0.06[b] (0.05-0.08)	a/b: **<0.002** b/b: 0.22
TSH-BAW	0.009[a] (0.008-0.009)	0.06[b] (0.04-0.07)	0.05[b] (0.04-0.07)	a/b: **<0.001** b/b: 0.87

Results are described as median (range). Results in the same row that are not connected by the same letter are significantly different. Reference interval: TT4 (9-46 nmol/L), TSH-CLIA (0.03-0.3 ng/mL) and TSH-BAW (0.008-0.3 ng/mL).

Table 2 – Proportions of suppressed thyroid-stimulating hormone using the Immulite 2000 canine assay (TSH-CLIA) and the novel feline-optimized assay (TSH-BAW) in euthyroid healthy and euthyroid cats with NTI

	Euthyroid healthy cats *(n = 32)*	**Euthyroid cats with NTI *(n = 33)***	**Total *(n = 65)***	*P* - value
TSH-CLIA	4/32 (12.5%)	8/33 (24.2%)	12/65 (18.5%)	0.34
TSH-BAW	1/32 (3%)	1/33 (3%)	2/65 (3%)	1.0
P - value	0.35	**0.026**	**<0.01**	

Proportions were not statistically different between each group (euthyroid healthy cats, euthyroid cats with NTI, and the total of all euthyroid cats). The proportions were significantly different between both assays for the euthyroid cats with NTI and the total of all euthyroid cats. Reference interval: TSH-CLIA (0.03-0.3 ng/mL) and TSH-BAW (0.008-0.3 ng/mL).

Table 3 – Concurrent diseases of euthyroid cats with NTI divided by severity

	Non-thyroidal illnesses
Group 1 – mild diseases *(n = 15)*	CKD (9), DM (2), chronic pancreatitis (1), CE (2), FIV+ (1), chronic nasal disease (2), fever (1), UTI (1), colonic mass (1)

Group 2 – severe diseases ***(n = 14)***	Acute or worsened gastrointestinal illness (2), round cell neoplasia (1), FUO (1), acute pancreatitis/cholangiohepatitis (3), pyelonephritis (1), DKA (3), systemic fungal disease (1), blood loss anemia (1)
Group 3 – severe diseases leading to non-survival ***(n = 4)***	Round cell neoplasia (1), pancytopenia (1), sepsis/bacteremia (2), secondary HL (1 – same as sepsis/bacteremia)

Abbreviations: Chronic kidney disease (CKD), diabetes mellitus (DM), chronic enteropathy (CE), feline immunodeficiency virus positive (FIV+), urinary tract infection (UTI), fever of unknown origin (FUO), diabetic ketoacidosis (DKA), hepatic lipidosis (HL)

Table 4a – Proportions of suppressed thyroid-stimulating hormone using the Immulite 2000 canine assay (TSH-CLIA) and the novel feline-optimized assay (TSH-BAW) in euthyroid cats with NTI divided by disease severity

	Group 1 ***(n = 15)***	**Group 2** ***(n = 14)***	**Group 3** ***(n = 4)***	*P* - value
TSH-CLIA	2/15 (6.7%)	5/14 (35.7%)	1/4 (25%)	0.34
TSH-BAW	0/15 (0%)	1/14 (7.1%)	0/4 (0%)	0.5
P - value	0.48	0.16	1.0	

Proportions were not significantly different between each group nor between assays.

Table 4b – Proportions of suppressed thyroid-stimulating hormone using the Immulite 2000 canine assay (TSH-CLIA) and the novel feline-optimized assay (TSH-BAW in euthyroid cats with NTI divided by disease severity

	Group 1 (mild diseases) ***(n = 15)***	**Groups 2 + 3 (severe diseases)** ***(n = 18)***	*P* - value
TSH-CLIA	2/15 (6.7%)	6/18 (33.3%)	0.24
TSH-BAW	0/15 (0%)	1/18 (5.6%)	1.0
P - value	0.99	**<0.01**	

Proportions were not different between each group (group 1 – mild diseases and group 2+3 – severe diseases). The proportions were significantly different between both assays for the group 2+3 – severe diseases.

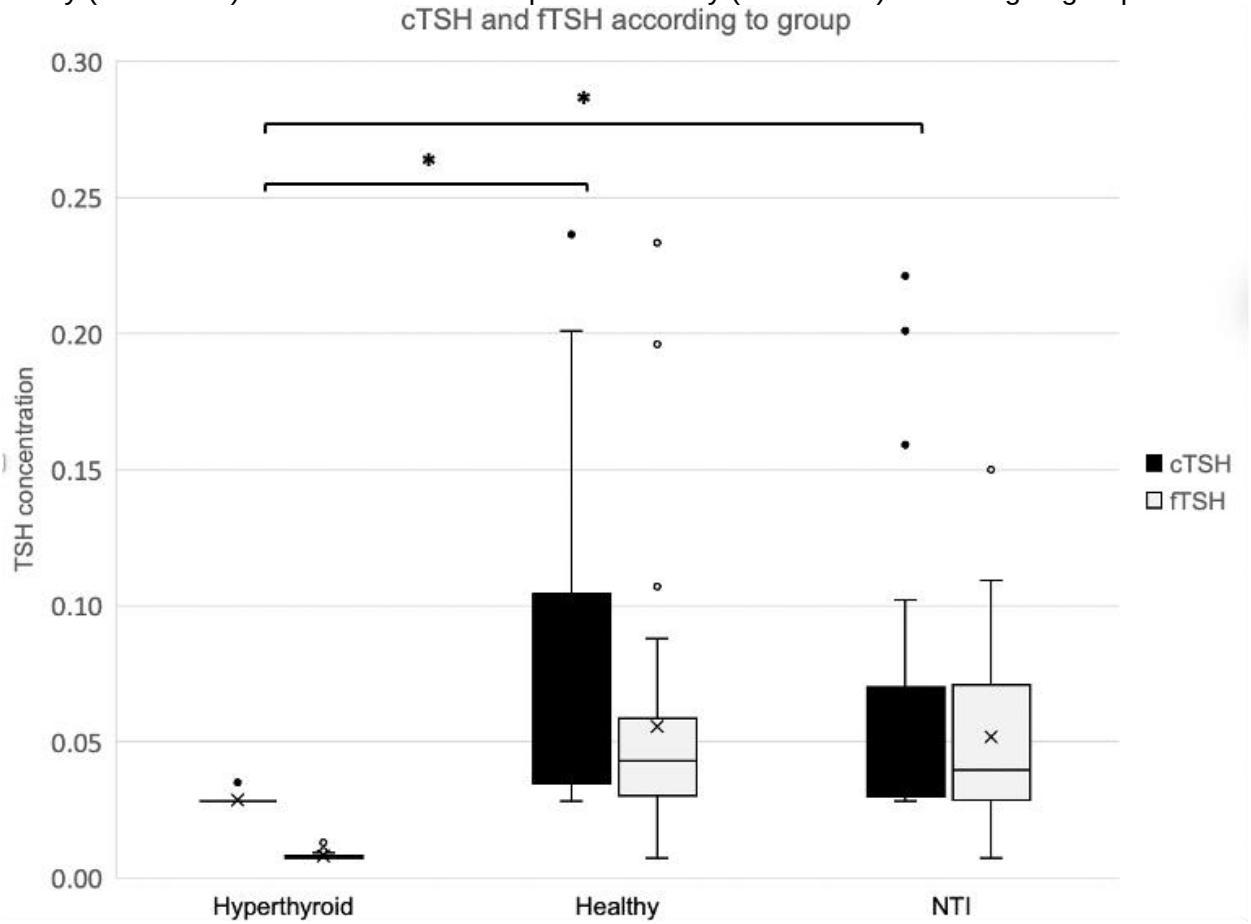
Table 4c – Proportions of inappropriately suppressed thyroid-stimulating hormone using the Immulite 2000 canine assay (TSH-CLIA) and the novel feline-optimized assay (TSH-BAW) in euthyroid cats with NTI divided by disease severity

	Group 1+2 (survivors) ***(n = 29)***	**Groups 3 (non-survivors)** ***(n = 4)***	*P* - value
TSH-CLIA	7/29 (24.1%)	1/4 (25%)	1.0
TSH-BAW	1/29 (3.4%)	0/4 (0%)	1.0
P - value	**0.03**	0.99	

Proportions were not different between each group (group 1+2 – survivors and group 3 – non-survivors). The proportions were significantly different between both assays for the group 1+2 – survivors.

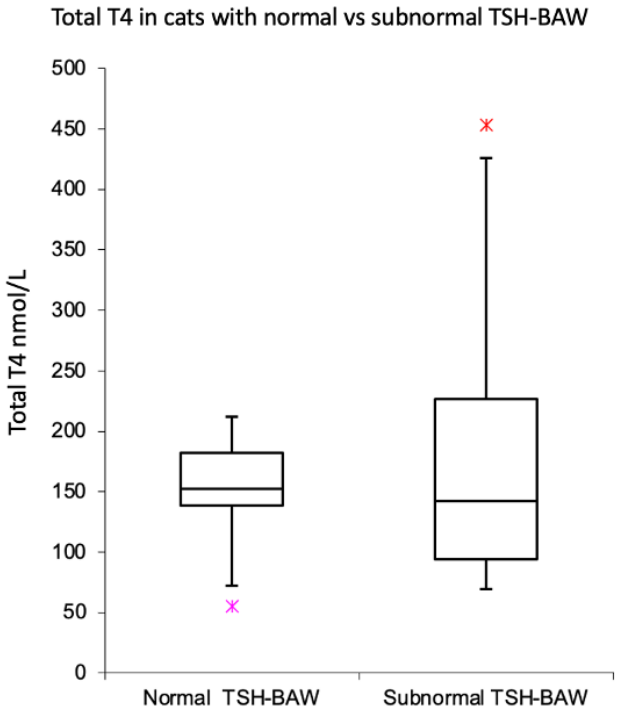
APPENDIX 2 – FIGURES

Figure 1 – Thyroid-stimulating hormone (TSH) concentration using the Immulite 2000 canine assay (TSH-CLIA) and the novel feline-optimized assay (TSH-BAW) according to group



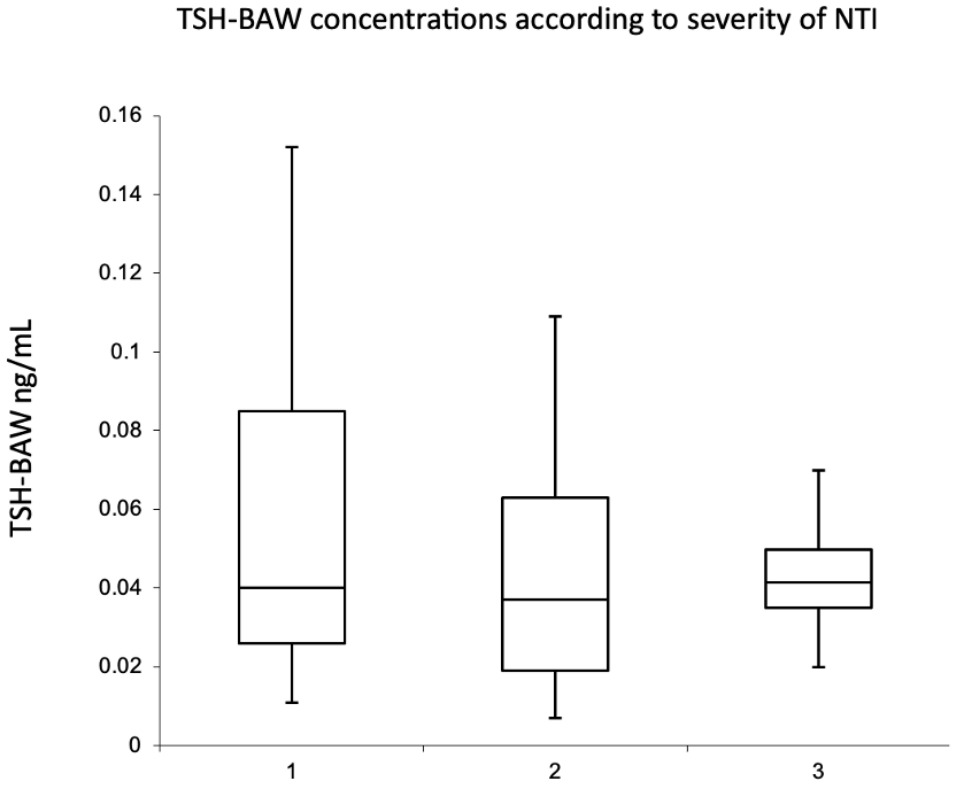
Median thyroid-stimulating hormone concentration (TSH) concentrations of hyperthyroid cats (Hyperthyroid), euthyroid healthy cats (Healthy) and euthyroid cats with non-thyroidal illness (NTI). Significant difference is marked by an asterix. The median TSH concentrations of the hyperthyroid cats were significantly different than both euthyroid groups (Healthy and NTI) with both assays (P<0.01). The median TSH concentrations of Healthy and NTI groups were not different with both assays (TSH-CLIA P=0.22, TSH-BAW P=0.87).

Figure 2 – Total thyroxine (TT4) concentration in hyperthyroid cats that had a normal TSH-BAW concentration vs subnormal TSH-BAW concentration



There was no significant difference (P=0.834). Asterix denotes outliers.

Figure 3 – Thyroid-stimulating hormone (TSH) concentrations using the novel assay (TSH-BAW) in euthyroid cats with nonthyroidal illnesses (NTI) according to their severity



Median thyroid-stimulating hormone concentration (TSH) concentrations of euthyroid cats with NTI divided by disease severity (group 1, group 2, and group 3). There was no statistical difference between each group (P=0.70).

CHAPTER 1 – LITERATURE REVIEW

Thyroid physiology

A. Thyroid structure and function

The thyroid gland is located in the ventral neck, with separate lobes on each side of the trachea in the cat. It contains two types of endocrine cells: follicular cells and parafollicular cells (or C cells). The basic functional unit of the thyroid is the follicle, composed of a single layer of thyroid epithelial cells and intraluminal colloid. The colloid contain thyroglobulins (Tg), a large glycoprotein produced by the thyroid follicular cells that is essential for the synthesis of thyroid hormones. The parafollicular cells (C cells) are located in the interstitium between the follicles, and are responsible for the production of calcitonin.(1-3) The C cells and their product calcitonin help regulate calcium metabolism.

During embryological development, the follicular cells originate from the pharyngeal epithelium. It then descends along the neck to its final position. During its descent, the thyroid remains connected to the pharynx by the thyroglossal duct, where remnants of thyroid tissue may be left. Similarly, accessory thyroid tissue in the mediastinum can be explained by the close embryologic relation of the thyroid to the aortic sac.(1, 3)

B. Hypothalamus-Pituitary-Thyroid axis

The hypothalamus-pituitary-thyroid (HPT) axis is a multi-loop feedback system responsible for thyroid homeostasis. The hypothalamus and pituitary gland are in close anatomical contact.(1-5)

The hypothalamus is a neuroendocrine structure located in the diencephalon. Special hypophysiotropic neurons in the paraventricular nucleus of the hypothalamus are responsible for the production of thyrotropin releasing hormone (TRH), which is then stored at the nerve ending. In response to specific stimuli, TRH is released into the median eminence, an extension of the hypothalamus into the pituitary stalk. The pituitary stalk is the functional link between the hypothalamus and the anterior pituitary. It contains the hypothalamic-hypophyseal portal blood system connecting both organs. Thyrotropin releasing hormone is transported to the anterior pituitary via this blood system.(4, 5) The anterior pituitary gland contains five types of cells which all have specific hormonal function. Thyroid releasing hormone act on thyrotropes, which are the cells responsible for thyroid homeostasis. The action of the thyrotropes leads to production and secretion of thyrotropin (or thyroid stimulating hormone (TSH)). In turn, TSH stimulates thyroid follicular cells to produce triiodothyronine (T3) and thyroxine (T4) via a G-protein-linked receptor and cAMP second messenger pathway.(1, 2, 4, 5)

The HPT axis is regulated by negative feedback via the plasma concentrations of T3 and T4. High concentrations of T3 at the hypothalamic and pituitary levels inhibit the synthesis of both TRH and TSH (long feedback). Thyroxine is converted into T3 by 5'-deiodination mainly in the peripheral tissue in cats.(3, 6, 7) A direct negative effect of T4, independent of T3, has also been reported.(8) Increased concentration of TSH also suppresses the hypothalamic production of TRH

(short feedback) as well as the further pituitary synthesis of TSH (ultra-short feedback).(1, 2, 4, 5) Other extrathyroidal factors are also known to positively or negatively affect the HPT axis, including fasting, stress, concurrent illnesses, hormones [cortisol, melanocyte-stimulating hormone (MSH), leptin, growth hormone (GH), MSH, leptin, GH, ghrelin, prostaglandins], drugs, neurotransmitters (dopamine) and cytokines (TNF-α, IL-1, IL-6). In humans, thyroid hormones and TSH concentrations are also influenced by the circadian rhythm, with peaks at certain time points of the day.(1, 2, 5, 9, 10) In addition, intrathyroidal autoregulatory mechanisms are present in situations of abnormal iodine concentration. Iodine insufficiency leads to decreased Tg iodination, decreased thyroid hormone synthesis, decreased thyroid sensitivity to TSH, and increased ratio of T3/T4 secretion.(1, 2) With iodine excess, there is a decreased expression of the genes encoding thyroid peroxidase (TPO) and Sodium-Iodine Transporter (NIS) in order to avoid hyperthyroidism.(1)

C. Production of thyroid hormones

The two thyroid hormones produced by the thyroid gland are T3 (3,5,3'-L-triiodothyronine) and T4 (3,5,3',5'-L-tetraiodothyronine). Iodine is required for their synthesis, which comes entirely from the diet. The thyroid gland is the only organ that can bind iodine organically. Thyroid hormones synthesis can be divided into the five steps listed below.(1-3, 5, 11)

The first step is the active transport of iodide from the extracellular fluid into thyroid follicular cells. This is done by the Sodium-Iodine Transporter (NIS) located on the basal membrane, which derives its energy from a Na-K-ATPase pump.(1-3, 5, 11) The second step includes Oxidation and Organification. Transport of iodine into the follicular lumen is facilitated by the protein pendrin. Iodine is oxidized by the enzyme thyroid peroxidase (TPO) and incorporated into the tyrosine residues of Tg. These actions take part at the apical membrane. The iodinated tyrosine residues formed are monoiodotyrosine (MIT) and diiodotyrosine (DIT), containing one or two iodine ions respectively. This process is called organification.(1-3, 5, 11) The third step is the oxidative coupling of the MIT and DIT to form the thyronines (T3 and T4). Coupling of two DIT leads to production of T4, and coupling of one MIT and one DIT results in production of T3. This reaction is also catalyzed by TPO.(1-3, 5, 11) The fourth step is the tansport of Tg back into the thyroid follicular cells by endocytosis or pinocytosis. In the cytoplasm, each colloid droplet fuses with lysosomes as they move towards the basal membrane. The lysosomal enzymes hydrolyze the bonds between the iodinated residues and Tg. This action releases T3, T4, MIT and DIT into the cytoplasm.(1, 2, 5, 11) The fifth and final step is the diffusion of T3 and T4 into the circulation, and de-iodination of the free iodotyrosine (MIT and DIT). The iodine is then recycled and reused by the thyroid follicular cells. A small, insignificant amount of Tg is also released into the circulation in healthy subjects.(1, 2, 5, 11) In opposition to other species, the feline thyroid gland does not contain the deiodinase enzyme D1. Therefore, conversion of T4 into T3 is mostly done locally in peripheral tissue.(3, 6, 7) This is where the majority of T3 is produced.

Thyroid hormones are highly protein bound, with a minimal number of them in their free form (<0.05% fT4 and 0.5% fT3)(1). The thyroid binding proteins include a high-affinity thyroxine-binding globulin (TBG), which is found only in dogs and humans, thyroxine-binding prealbumin (TBPA), also called transthyretin, albumin, and in a minimal amount of lipoproteins and

transthyretin. Due to the lack of TBG in cats, the main binding protein is transthyretin. Thyroxine is significantly more highly bound to proteins than T3. Therefore, T4 has a lower metabolic clearance rate and a longer half-life. For this reason, the majority of thyroid hormone produced by the thyroid gland is T4.(1, 2)

D. Mechanism of action and metabolism of thyroid hormones and TSH

Only free thyroid hormones can enter cells and exert a biologic effect. T3 is three to five times more potent than T4, and is therefore the main biologically active thyroid hormone. This is mainly due to its higher affinity for the nuclear receptor (15 fold), but also a quicker entry into the cell and onset of action. Between 40% and 80% of T4 is transformed into T3 by deiodination in local tissue.(1, 2)

Thyroid hormones exert their biologic effect through genomic and nongenomic mechanisms. Primarily, they act on a nuclear receptor present in almost all cells of the body. This nuclear thyroid hormone receptor (TR) belongs to the steroid-thyroid-retinoid receptor family, which exists in four forms in cats. The action of thyroid hormones on TR influences the expression of many genes coding for different metabolic processes. Recently, it was found that thyroid hormones also act on receptors in the membrane (integrins) and mitochondria of almost all cells of the body.(1-3) These nongenomic effects are thought to contribute to the basal setting of cells.(1-3) Binding to mitochondrial receptors leads to activation of adenine nucleotide translocase (ANT), which influences energy production via non-shivering thermogenesis and ATP production from oxidative phosphorylation.(12) Activation of the integrin receptors leads to proliferative actions and affects the activity of ion channels.

Due to their action on almost all cells in the body, thyroid hormones are part of the metabolic processes of the entire organism. They stimulate calorigenesis, and are therefore essential for the regulation of the basal metabolic rate and thermoregulation. Thyroid hormones play a critical role in fetal development and growth. They stimulate carbohydrate, lipid, and protein metabolism. Thyroid hormones lead to increased activity of Na-K-ATPase pumps as well as increased mitochondria size and number. Some of their effects include positive chronotropy and inotropy, increased oxygen consumption, stimulation of erythropoiesis, and increased bone turnover. As this is a non-exhaustive list of all the numerous functions of the thyroid hormones, it can be concluded that T3 and T4 stimulate the metabolic processes of all cells in the body.(1, 2, 4)

In most species, inactivation of T3 and T4 is mainly achieved via deiodination, which is performed by deiodinase enzymes (D1, D2 and D3). Deiodinase enzyme D3, an inner ring 5-deiodinase, is the main enzyme leading to inactivation of T3 and T4 by transformation into metabolically inactive reverse T3 (rT3) and 3,3'-diiodothyronine (3,3'-T2).(1-3, 6, 7) At this time, it is unclear if cats have the D3 enzyme. Considering the short half-life of thyroid hormones and the high iodine requirement in cats, D3 enzymatic activity is likely present.(3, 6, 7) The second major metabolic pathway of thyroid hormone inactivation is conjugation to soluble molecules (glucuronides and sulfates), and subsequent elimination in bile and urine.(1, 2)

Feline Hyperthyroidism

A. Description of the disease

Hyperthyroidism or thyrotoxicosis is defined as excessive production and secretion of thyroid hormones T3 and T4. In cats, it is due to a primary autonomous condition of the thyroid gland, with a benign adenomatous process (adenomatous hyperplasia or follicular cell adenoma) being the most common pathology. In 70% of cases, both thyroid glands are affected.(13) Functional thyroid carcinoma is a rare condition, seen in less than 3-5% of cases.(14-18) Ectopic thyroid disease is also uncommon with a prevalence of 4%.(19) Feline hyperthyroidism (FHT) is a progressive disease, similar to toxic nodular goiter in humans.(20) Other causes of hyperthyroidism reported in humans and/or in dogs include TSH-secreting pituitary adenoma(21, 22), ingestion of exogenous thyroid hormones(23, 24), and acute thyroiditis(25). These conditions have not been documented in cats.(1, 2) An autoimmune etiology was suspected in one older study(26), but that hypothesis was refuted by multiple reports, including a publication from the same investigators. (27-29)

Thyroid autonomy, or autonomous replication of thyroid follicular cells and of thyroid hormones synthesis, is the key to development of hyperthyroidism. It is believed that chronic stimulation of follicular cells with a high growth potential would lead to somatic mutations, and therefore to autonomy.(30-33) Several mutations involving different aspects of the thyroid follicular cells have been published in cats with hyperthyroidism. One study reported eleven mutations of the TSH receptor gene in thyroid nodules of hyperthyroid cats, of which five are also seen in humans with hyperthyroidism.(34) Other publications (*in vitro* and *in vivo*) have identified decreased expression of inhibitory G proteins(35, 36), and overexpression of the oncogene c-Ras(37) in thyroid nodules of hyperthyroid cats. Unfortunately, the underlying cause of those mutations remains unclear.

Hyperthyroidism is a the most common endocrinopathy affecting cats. The mean age at diagnosis is 12-13 years old, with a range of 4 to 22 years old. Feline hyperthyroidism is rarely diagnosed in young animals, with less than 5% of them diagnosed before 8 years of age.(13, 38-40) Hyperthyroidism causes a hypermetabolic state leading to systemic complications. Most common clinical signs include weight loss, polyphagia, hyperactivity, gastrointestinal signs (vomiting, diarrhea), polyuria/polydipsia, poor grooming, and behavior changes. The latter includes increased activity levels, anxiety and aggressiveness.(1, 2, 33) Less than 10% of hyperthyroid cats will be lethargic and have a poor appetite (“apathetic” or asymptomatic hyperthyroidism).(13, 40) In humans, this condition is mainly seen in older patients with concurrent diseases and/or therapy responsible for those symptoms.(41, 42) Advanced severe hyperthyroidism can also lead to lethargy and generalized weakness.

Hyperthyroidism has significant effects on the cardiovascular system, including positive chronotropy, reduced atrioventricular conduction times, and upregulated beta-adrenergic receptors. Hyperthyroid cats often have systolic heart murmurs (54%), tachycardia (42-66%), a gallop rhythm (12-15%) and other potential arrhythmias. Electrocardiographic abnormalities include increased R-wave amplitude on lead II (29-49%), atrial and ventricular arrhythmias (20%), prolonged QRS duration (16%), shortened Q-T interval (11%), and conduction disturbances (3%).

Echocardiographic abnormalities include myocardial hypertrophy (72%), enlarged left atrium (70%) and left ventricle (46%), and enhanced contractility (15-21%). They can also have an elevated myocardial marker Troponin I.(2, 13, 33, 43-46) Those changes are similar to those seen in cats with primary hypertrophic cardiomyopathy (HCM), however they rarely lead to congestive heart failure (<5%), and they mostly resolve once the hyperthyroidism is treated.(13, 33, 43-45) Heart failure was more commonly reported before the 2000s, likely due to the fact that FHT was diagnosed in a more advanced state(13, 46). Systemic hypertension (SH) is also reported in hyperthyroid cats, however a causality has not been clearly proven. Prevalence of SH is believed to be somewhat low, with most recent publications reporting a prevalence between 5-20%.(47-49), with one older study publishing a higher prevalence of 89%.(50) The pathophysiology of SH in FHT is unclear. Diastolic resistance is reduced due to decreased peripheral vascular resistance and the increase in cardiac output only mildly elevates the systolic blood pressure.(51) Hypertension does not always resolve after controlling hyperthyroidism.(48, 49) Interestingly, 20-25% of cats will develop SH after treatment of hyperthyroidism.(49) Target organ damage (TOD) due to FHT is also very uncommon.(51, 52) In summary, the association between FHT and SH is unclear, and could be the result of a comorbidity such as masked chronic kidney disease, or the "white coat effect" associated with the increased anxiety of hyperthyroid cats.(2, 33)

Hyperthyroidism increases glomerular filtration rate (GFR) by several mechanisms, including increased renal blood flow secondary to increased cardiac output, intra-renal vasodilation, decreased resistance of the efferent arteriole, activation of the renin-angiotensin-aldosterone system (RAAS), and increased tubuloglomerular feedback secondary to changes in tubular reabsorption. This increase in GFR, along with increased tubular secretion and decreased muscle mass, leads to reduced creatinine concentration.(33, 51, 53) Concomitant chronic kidney disease, which is common in senior cats (>30% in cats over 15 years old)(54), can therefore be missed. At time of diagnosis, about 10-25% of cats are azotemic.(38, 55, 56) Following a reduction in GFR upon a return to euthyroidism, , the prevalence of post-treatment azotemia increases to 15-50%.(38, 55-62) Predicting occult kidney disease in hyperthyroid cats is challenging, and most studies have not found a predictive blood work parameter. A recent paper reported that urine specific gravity (USG) is only mildly affected by hyperthyroidism, and that a concentrated urine capacity (>1.035) has a high sensitivity in predicting normal renal function after treatment.(63) Another effect of hyperthyroidism on renal function is the development of mild proteinuria. Since the mechanism is unclear, the latter is not associated with renal damage, and mostly resolves within 4 weeks after treatment.(56, 62)

B. Prevalence and etiology

Feline hyperthyroidism was first described by Peterson et al. in 1979 in a case series of five cats.(64) In 1980 and 1981, another case series of ten cats was published in the United States of America (USA), as well as a case report of one cat in New Zealand.(65, 66) Following those publications, FHT started to be recognized by veterinarians in several countries, and screening for the disease slowly became an important part of feline medicine.

The prevalence of FHT before its recognition in 1979 was suspected to be low, but some reports seemed to be contradictory. In 1964, a histological study of the feline thyroid gland

reported that thyroid anomalies were common in domestic cats, and that typical clinical signs in some of those patients were suggestive of FHT.(17) However, a pathology review study came to the opposite conclusion: Of several thousands of feline necropsies performed at the Animal Medical Center (AMC) in New York City between 1970 and the first diagnosis of FHT in 1977, the incidence of gross thyroid enlargement was rare at an average of 1.9 cats per year.(67)

In 1983, the first reported incidence of FHT was published by Peterson et al. in New York City. Three new cases were diagnosed per month, with 131 diagnoses over a 3.5 year period.(13) During a similar timeframe, at the University of California, a total of 125 cats were diagnosed with FHT over a 5 year period.(2) Already in the 1990s and 2000s, FHT was recognized as a common disease of middle-aged and senior cats. Since it was first discovered, the prevalence of FHT in North America has seen a significant increase.(2, 68, 69) The prevalence was as low as 0.1-0.3% between 1978-1982, and increased to 3-4.5% in publications from 1985 and 1993-1997.(13, 39, 64, 70, 71) The prevalence of FHT in cats over 8-10 years of age was reported in the 2000s in various regions of the world, with evidence of regional differences: 11.4% in Germany(72), 16.4% in United Kingdom (UK)(73), 20.1% in Spain(73), 3.9% in Hong Kong(74), and 8.9% in Japan(75). Since then, the prevalence of hyperthyroidism has remained around 10-20% in cats over 10 years old, with some regional variation.(1, 2, 68, 76-78) Feline hyperthyroidism is considered the most common endocrinopathy in cats in this age range.

Although increased recognition of FHT and improvement of geriatric feline medicine play a role in the increased prevalence of the disease, researchers suspect other factors are also contributing. Epidemiological studies have reported several risk factors for FHT, including genetic predispositions as well as nutritional and environmental exposure leading to thyroid dysfunction.(1, 2) Multiple publications have shown that pure breeds (especially Siamese and Himalayan breeds) are protected from the disease.(70, 77, 79-81) Female cats seem to be over-represented in some studies(39, 80), but a sex predilection is not consistently reported.(74, 77, 81, 82)

Eating mainly canned food has been associated repeatedly with a higher risk of developing FHT.(3, 39, 70, 79-83) As the etiology of this nutritional factor remains unclear today, it is hypothesized that nutritional excesses and deficiencies as well as consumption of goitrogens (i.e. thyroid disruptors) are causative.(2) Dietary iodine concentration is one of the most studied nutritional factors. Indeed, deficiency and excess in iodine, especially with dramatic fluctuations, are known to increase the risk of toxic nodular goiter in humans.(84-86) In cats, some publications have found a correlation between lower concentrations of iodine and development of FHT.(39, 81) Also, iodine concentration is highly variable in commercial cat diets, especially canned food, and supplementation in iodine has decreased over the last 30 years.(87-89) However, there is not enough data to establish a cause and effect relationship between iodine deficiency or dramatic fluctuation in iodine intake and FHT. Selenium excess has also been studied due to its role in thyroid homeostasis, but no correlation has been found between selenium concentration and FHT.(90-92) The effect of high dietary moisture has been evaluated showing a potential small effect of water content on thyroid function, but a definitive clinical statement cannot be concluded from this study.(90)

Consumption of goitrogens, or compounds that disrupt thyroid function, is another risk factor that is likely important in FHT pathogenesis. Goitrogens can come from the diet and/or the environment. Soy isoflavones are known to inhibit thyroid enzymes (TPO and 5'-deiodinase), leading to decreased T3 concentration and secondary increase in TSH. The latter results in increased synthesis of thyroid hormones, and therefore elevation of T4 and normalization of T3.(2, 93) The thyroid disruption seen secondary to soy is exacerbated by iodine deficiency, and there is likely an interaction between different risk factors in the pathogenesis of FHT.(93) Soy isoflavones are present in multiple dry food commercial feline diets, which is not consistent with the increased risk of FHT in cats eating canned food. Other compounds that are known goitrogens include bisphenol A (BPA), polychlorinated diphenyls (PCB), polybrominated diphenyl ethers (PBDE), dioxins, perfluorinated chemicals, phthalates, and perchlorates.(2) All of these compounds can disrupt thyroid function by several mechanisms, including inhibition of enzymes and blockade or activation of receptors.(2) The structure of BPA, PBC and PBDE is highly similar to T4.(69) Bisphenol A is used to make epoxy resins that compose the interior lining of metal cans. Migration of BPA into food has been proven in both human and pet food products.(94, 95) It is suspected that BPA might at least partly explain the association between canned food and FHT.

Indoor housing and exposure to different chemical products (mainly fertilizers, herbicides, insecticides and cat litter) have also been associated with an increased risk of developing FHT in multiple publications.(70, 79-81) House cats have elevated plasma concentration of PBDEs(96), and a recent study showed higher concentrations of different types of PBDE and PCB in the plasma of hyperthyroid cats.(97) This study supports the hypothesis of goitrogens in the pathogenesis of FHT and suggests the environment where cats live has an effect on the development of this disease.

B. Early/subclinical hyperthyroidism

Subclinical hyperthyroidism (SCH) is defined in humans as low TSH concentration in conjunction with normal TT4.(98, 99) Despite being subclinical, this entity can be associated with systemic complications in humans, especially cardiovascular disorders, and treatment may be required. It can also progress into clinical hyperthyroidism.(98, 99) Diagnosis can be challenging, as TSH can be decreased due to other factors, including nonthyroidal illness syndrome (NTIS) and drug-mediated suppression.

In cats, subclinical hyperthyroidism has not been clearly defined nor studied as it has been in humans. Subclinical, early, and mild hyperthyroidism are sometimes used synonymously. Cats classified into these categories generally have normal or slightly elevated total T4 and suppressed TSH concentrations. The presence of clinical signs in these cats are generally absent to mild. As discussed later, using TSH concentrations to define these cats has been problematic given the limitations of the TSH-CLIA assay (see C. Diagnosis). In some studies, severity of clinical signs, thyroid hormone concentrations, and thyroid scintigraphy are used to determine if cats have subclinical or mild hyperthyroidism.(100, 101)

One publication has reported the presence of low TSH concentration with normal T4 value, suggestive of SCH.(100) Histopathology of the thyroid gland of those cats revealed a higher prevalence of nodules. However, limitations were that most of those cats had non-thyroidal illness with a predominance of kidney disease, the low TSH was based on only one blood sample, and it was performed on a canine assay. Due to the canine assay being the only assay available for measurement of TSH, its low sensitivity makes it impossible to know if the TSH was truly decreased in those cats.. In a later study by the same authors, cats with an undetectable TSH were more at risk of progressing to clinical hyperthyroidism with an odds ratio of 39.(83) Based on their data, 28% of cats were defined as having SCH.(83) Considering the limitations of this study, it is likely overestimating the true prevalence of SCH.

Other studies have used a severity score system to define SCH. This scoring system is based on the TT4 and TT3 concentrations, the measured thyroid tumor volume on scintigraphy, the percent thyroidal uptake of sodium ^{99m}Tc-pertechnetate, and the 24-hour thyroid I^{131} uptake measurement.(101-103) Based on this system, about half of the cats have a mildly elevated TT4, and about a quarter have a normal TSH concentration.(101)

As seen in humans, the presence of a thyroid goiter is common in euthyroid cats. Between 38-76% of senior cats without overt hyperthyroidism have a palpable thyroid slip.(104-106) Histologically, up to 85% of those thyroid glands had lesions consistent with nodular hyperplasia or adenoma.(107, 108) A significant amount of euthyroid cats with thyroid nodules end up developing overt hyperthyroidism within months to years.(83, 100, 108) Having a thyroid goiter does not coincide with hyperthyroidism, but cats with a thyroid slip are at an increased risk of developing the disease.(83, 100) It is important to remember that most hyperthyroid cats (80-90%) have a thyroid nodule on palpation.(2, 13, 38, 40)

C. Diagnosis

The diagnosis of FHT typically includes measurement of thyroid hormones in combination with compatible clinical signs and physical examination findings. The thyroid hormones that can be evaluated include total T4, total T3, free T4, and TSH.

The primary method for diagnosing FHT is by measuring the serum concentration of total T4 (TT4). It is inexpensive, simple, and leads to a diagnosis of hyperthyroidism in over 90% of the cases.(38, 109) It has a high sensitivity (91-96.5%) and specificity (93-100%) for diagnosis of FHT, making it the screening test of choice.(2, 13, 38, 40, 109) Hyperthyroid cats can have a normal TT4 concentration for several reasons, including normal daily fluctuation of this hormone in the blood, presence of subclinical/early disease, or presence of a concurrent illness, termed nonthyroidal illness syndrome (NTIS). About 10% of hyperthyroid cats have a normal TT4 concentration, with approximately 80% of these cats having mild hyperthyroidism and 20% having concurrent NTIS.(9, 33, 110-112) The effect of NTIS on thyroid function is discussed in depth in the next chapter of this document. Total T4 can be measured with four different assays: Radioimmunoassay (RIA), chemiluminescent enzyme immunoassay (CLIA), point-of-care (POC) enzyme-linked immunosorbent assay (ELISA), and enzyme immunoassay (EIA).(113) Other human assays are not recommended. Radioimmunoassay is considered the gold standard, but

is limited by the need for radioactive metabolite and lack of automation.(106, 110, 113, 114) In comparison, CLIA is considered very similar(115, 116), however ELISA and EIA are less reliable.(113) The ELISA assay shows discordant results in up to 56% of cases, and is therefore not considered accurate.(117) The EIA correlates better, but discordance is seen in 24% of cases.(113, 118) Both of these assays can therefore lead to false positive as well as false negative results, impacting clinical decision making. If a false positive TT4 result is a concern using either of these methods, then measuring TT4 using the RIA method is recommended.

Measurement of total T3 (TT3) is also highly specific, but its lack of sensitivity reduces its utility. TT3 remains in the normal reference interval in over 30% of hyperthyroid cats.(38, 109) This is partly due to a compensatory decrease in peripheral conversion of T4 into T3 secondary to hyperthyroidism.(110) For this reason, TT3 is rarely used for diagnosis of FHT. If measured, it should be interpreted in conjunction with a TT4 level.

Measurement of free T4 (fT4) is more sensitive than TT4 for FHT, with elevation of fT4 in over 98% of hyperthyroid cats.(109) As it is less affected by NTIS than TT4, fT4 will be elevated in 95% of cases where the TT4 is within the reference range.(109) However, fT4 is associated with significant limitations, including the need for special measurement assays (equilibrium dialysis or ultrafiltration), the increased risk for spurious errors, and a critical lack of specificity (as low as 84%).(109, 110, 119-121) If fT4 concentration is not commonly reduced secondary to NTIS, the opposite is not true: NTIS can lead to increased values of fT4. Up to 30% of euthyroid cats with a NTIS have elevated fT4 level.(109, 122) Endocrinologists therefore recommend against the use of fT4 alone for the diagnosis of FHT. As the addition of fT4 does not add diagnostic value to TT4 concentration, it is rarely performed.(109, 110, 123) There are two main ways to measure fT4, either by equilibrium dialysis (ED) or via a chemiluminescent enzyme immunoassay (CLIA). Equilibrium dialysis or ultrafiltration are required to truly determine the fT4 concentration, and therefore ED is considered the gold standard. This has been well distinguished in dogs with thyroid diseases.(124-126) Although there is good correlation between fT4 measured via CLIA and ED, ED remains superior in hyperthyroid cats, both before and following therapy. Compared to ED, CLIA had a lower sensitivity for diagnosis of FHT, and led to overdiagnosis of iatrogenic hypothyroidism.(126) As ED is more expensive and takes longer to measure, it remains the test of choice for measurement of fT4.

In the absence of a feline-specific assay, serum TSH concentration is usually measured with chemiluminescent canine immunoassays (TSH-CLIA) (Immulite Canine TSH assay; Siemens; Malvern, PA, USA USA). For diagnosis of feline hyperthyroidism, the TSH-CLIA has an excellent sensitivity (97-99%), but a low specificity (70-85%), significantly limiting its usefulness.(2, 83, 101, 113, 127) This poor specificity is explained by its inability to differentiate low-normal from truly decreased TSH values, both below the low limit of detection of 0.03 ng/mL. About 25%-30% of euthyroid cats have a suppressed TSH (<0.03 ng/mL).(101, 127) The positive predictive value (PPV) of this assay is very low at 21.7%.(101) For this reason, TSH alone is not recommended for screening of feline hyperthyroidism. However, combination of TSH with TT4 or fT4 increases the specificity to 99%.(127) A novel TSH assay with a lower limit of detection has recently been developed for feline TSH measurement (TSH-BAW) (Truforma Feline-optimized

TSH assay; Zomedica; Ann Harbor, MI, USA). This assay uses bulk acoustic wave (BAW) technology which detects shifts in radio frequency on the sensor surface. The TSH molecules present in the sample bind to a capture monoclonal antibody on the sensor as well as a monoclonal antibody in solution, forming a sandwich complex. An enzyme binds to this complex, immobilizing it to the sensor surface and converting an enzymatic substrate to an insoluble product, which accumulates on the sensor. This change in weight on the sensor surface is detected.(128) The BAW technology is highly sensitive and allows a lower limit of detection of 0.008 ng/mL, significantly lower than the TSH-CLIA assay.(128-130) A TSH of 0.01 ng/mL can differentiate euthyroid and hyperthyroid cats, with 12% of cats with a normal TSH-BAW (≥ 0.01 ng/mL) having a suppressed TSH-CLIA (<0.03 ng/mL).(128) Based on a recent study evaluating this assay, the test sensitivity and specificity for diagnosis of feline hyperthyroidism are 91.1% and 98.9%, respectively. It also has a high positive predictive value (PPV) of 86.9%.(101) However, this study did not evaluate extensively the effect of NTI on the TSH-BAW assay, with only a small group of 12 cats with CKD. Considering that 20-30% of hyperthyroid cats with a high-normal TT4 suffer from concurrent diseases, it is essential to determine how the TSH-BAW assay is affected by NTI before recommending it as a test of choice.

Dynamic tests have been evaluated in the past for the diagnosis of FHT. These include the T3 suppression test, the TRH stimulation test, and the TSH stimulation test. The aim of those tests is to diagnose early hyperthyroidism when TT4 and fT4 are within reference range or unhelpful. With the T3 suppression test, a significant overlap exists between euthyroid and hyperthyroid cats.(131-133) With the TRH stimulation test, values between 50-60% are equivocal(110, 134, 135), and administration of TRH commonly causes cholinergic reactions including severe salivation, nausea, vomiting, diarrhea, tachypnea and micturition.(136-139) The TSH stimulation test has a poor diagnostic performance, with a strong overlap between results of euthyroid and hyperthyroid cats.(140) The accuracy of all three tests is reduced with the presence of NTI.(141) In summary, dynamic tests can potentially be useful for diagnosing the early form of FHT, however they are rarely needed.(110, 135)

The best diagnostic test available for diagnosis of FHT is radioisotope uptake of the thyroid visualized via scintigraphy. Increased uptake of radioactive iodine (I^{123} or I^{131}) or pertechnetate ($^{99}TcO4^-$) can be confirmed by the thyroidal percentage of uptake or by the thyroid-to-salivary ratio. It correlates strongly with the concentration of thyroid hormones, and is highly sensitive (99%). Scintigraphy is also beneficial in identifying the extension of the disease (unilateral vs. bilateral, presence of ectopic functional thyroid tissue), and in raising the index of suspicion of a thyroid carcinoma.(16, 19, 142, 143) The limitations of this test are mainly related to its need for ultra-specialized equipment and the biosecurity requirements of dealing with radioisotopes. Heavy sedation or general anesthesia might be required for the performance of this test. Therefore, as scintigraphy is the gold standard in diagnosing FHT, its use remains mostly limited for patients assessment prior to thyroidectomy or radioactive iodine therapy.(110)

D. Management

Feline hyperthyroidism can be managed with both definitive and non-definitive therapies. Choice of treatment depends on the characteristics of hyperthyroidism, the status of the patient, as well as the owners' preferences.

Non-definitive (or reversible) treatments include oral anti-thyroid drugs and iodine-restricted diets. These therapies control hyperthyroidism by inhibiting the production and/or action of thyroid hormones. They are not cytotoxic to the thyroid adenomatous disease, and therefore do not resolve the underlying cause of the hyperthyroidism. Stopping this type of therapy will lead to relapse of the clinical disease.(2, 3, 144)

1. Oral anti-thyroid medications, also called thioureylenes, exist in three different forms: methimazole, carbimazole and propylthiouracil (PTU). All thioureylenes act by inhibiting the action of TPO, the enzyme required in oxidation of iodine, organification, and coupling of the iodinated tyrosine residues to form T3 and T4.(145, 146) Propylthiouracil is not recommended in cats anymore due to important adverse effects.(147, 148) Anti-hyperthyroid drugs are the most popular first-line therapy for treatment of FHT. Owners of hyperthyroid cats will be offered this treatment option in 92% of cases, and 93% of cats will be treated with thioureylenes at some point in the course of their disease.(149) Control of the hyperthyroidism is achieved in about 75% of cases.(150) However, the primary thyroid disease will continue to grow, and may become resistant to anti-thyroid drugs with time. In a large cross-sectional study of 2096 cats, 19.3% of cats became refractory to methimazole and were suspected to have progressed to a thyroid carcinoma within 4-6 years (vs. 0.4% within one year of diagnosis).(151) Survival time is lower in cats treated with anti-thyroid medications compared to radioactive iodine (2 years vs. 4-5.3 years).(55) Other than progression of the primary thyroid disease, inconveniences of anti-thyroid drugs include their adverse effects –dose-dependent vomiting and anorexia (20-25%), self-induced excoriations (up to 12%), myelosuppression (16 to 35%), hepatopathy (3%), bleeding diathesis (3%), and acquired myasthenia gravis (few reports only) –, the need for check-ups in the long term, the need to pill the cat for the rest of its life, and its teratogenic potential.(3, 144, 150, 152) A topical formulation of methimazole has been proven to be effective, and can be beneficial in cats that are difficult to pill and to reduce the prevalence of gastrointestinal adverse events.(153, 154)

2. Iodine-restricted diet is the other reversible therapy for FHT. As iodine is an essential component of thyroid hormones production, severe iodine restriction (<0.3 mg/kg) significantly decreases the concentrations of both T3 and T4 in cats.(155-160) At this time, there is only one commercial iodine-restricted diet for management of FHT: *Hill's Prescription Diet y/d*. Dietary management has the lowest success rate in controlling hyperthyroidism, estimated at about 50%.(150) It fails to normalize thyroid hormones concentration in 30% of cats, and when they decrease back to the reference interval, they usually stay in the high normal range. Subsequently, clinical signs and systemic effects of hyperthyroidism are not completely controlled in most cases.(155-162) Other important inconveniences of dietary therapy include the low palatability of the available commercial diet, its suboptimal protein composition for cats that are already muscle wasted, and the need to feed this diet exclusively.(162) In summary, the use of a iodine-restricted diet is considered the last therapeutic option for FHT, and should be reserved for cases where other treatments are not possible.(2, 3, 150)

Definitive options include radioactive iodine therapy and surgery (thyroidectomy). Both treatments offer a permanent cure by removal of the thyroid autonomous disease. They are however not reversible, and complications of these procedures are often permanent as well.(2, 3)

1. Radioactive iodine therapy (or I^{131} therapy) is considered the best treatment for FHT.(1-3, 150, 163, 164) This therapy is safer than surgery, has lower complication rates, is non-invasive, and is curative. Success rate of radioactive iodine therapy is over 95%, and survival time is higher.(55, 150, 164, 165) It is also financially beneficial: the cost of the procedure is upfront, but considered advantageous on the long term compared to antithyroid medications.(166) The mechanism of action of radioactive iodine therapy allows for specific destruction of the autonomous tissue, and is therefore beneficial for ectopic thyroid disease.(145, 163, 165) It is also the treatment of choice for cats with invasive/metastatic carcinoma.(18, 167, 168) The use of radioactive material requires the need for special licensing and facilities. Local, regional and national laws regarding radiation safety need to be respected. After receiving I^{131} treatment, cats must be hospitalized in a specific area until the radiation they emit is considered low enough, and specific guidelines must be followed by the owners for 2-4 weeks after discharge.(3, 164, 169) This period of hospitalization and quarantine can be a major concern for some owners(170). Cats with significant or unstable concurrent diseases should be excluded from receiving this therapy. Other inconveniences of I^{131} therapy include treatment failure and development of iatrogenic hypothyroidism. About 5% of cats fail their first I-131 treatment and require retreatment or alternative therapy (thyroidectomy or antithyroid medications).(165, 171-174) A 2021 study reported that all cats with a TT4 concentration >150 nmol/L (11.6 µg/dL) at time of discharge after I-131 therapy ultimately failed to become euthyroid.(174) Iatrogenic hypothyroidism, on the other hand, is fairly more frequent. The prevalence of iatrogenic hypothyroidism remains high and variable, ranging from 5-50% depending on the study.(102, 103, 164, 171-173, 175, 176) This disparity is partly due to the definition of hypothyroidism, time of follow-up, difference in dosing regimens, and age of the study. Iatrogenic hypothyroidism should be categorized as previously reported: overt hypothyroidism (T4 <1.0 µg/dL; TSH >0.30 ng/mL) vs. subclinical hypothyroidism (T4 = 1.0-3.8 µg/dL; TSH >0.30 ng/mL).(171, 177) Iatrogenic hypothyroidism can be only transient (about 30% of cases), with full recovery of thyroid function within 6-12 months, or definitive and require treatment. Long-term follow-up is needed as it can take up to 18 months for hypothyroidism to occur.(178) Iatrogenic hypothyroidism is rarely associated with clinical signs typical of the disease, but is clinically important due to its effect on the kidneys. Development or worsening of azotemia as well as reduced survival time have been associated with iatrogenic hypothyroidism.(56, 103, 175, 179) Supplementation with levothyroxine is recommended with those cats. At this time, using an individualized and/or low dose of I^{131} as well as selecting patients with an undetectable TSH concentration are the actions that can be taken to hopefully reduce the risk of iatrogenic hypothyroidism.(102, 103, 171) Despite those potential complications, the prognosis of radioactive iodine therapy is considered excellent.(1-3, 150, 170)

2. Thyroidectomy has a high success rate of over 90%, slightly below I^{131} treatment, and is the fastest way to resolve hyperthyroidism (24-48 hours after surgery).(14) It is however an invasive procedure that requires general anesthesia, is more expensive, and associated with a higher risk of complications.(14, 150, 180) Complications of thyroidectomy include iatrogenic

hypothyroidism, iatrogenic hypoparathyroidism, treatment failure, laryngeal nerve paralysis, Horner's syndrome, hemorrhage and infection. After bilateral thyroidectomy, patients will for sure be hypothyroid, and the risk of hypoparathyroidism is significantly increased.(14, 180-182) Life-threatening hypocalcaemia can occur, in which case in-hospital intensive care is required. Treatment failure can occur when thyroid tissue is left in situ during the procedure, when ectopic tissue is not identified (intrathoracic, base of the tongue), or when the thyroid tumor invades peripheral tissue.(3, 14, 18, 19, 180) Considering that thyroidectomy is less beneficial and more risky than radioactive iodine treatment, it is rarely recommended in the first place.

Non-thyroidal illness syndrome (NTIS)

A. Overview of NTIS

Non-thyroidal illness syndrome (NTIS), previously referred as euthyroid sick syndrome, is defined as changes in thyroid hormones concentration in sick patients in the absence of dysfunction of the hypothalamus-pituitary-thyroid axis.(183-187) Typical changes involve decrease in T3 +/- T4 concentration, and specificities regarding results of thyroid testing in each species will be discussed in the next section. Changes in thyroid values resolve with recovery of the underlying illness.(186, 188-190) The pathogenesis of NTIS is multifactorial, and has not been completely elucidated yet. Pathophysiological mechanisms include inadequate activity of the deiodinases D1, D2 and D3, decreased expression of thyroid hormone receptors, impaired binding to transport proteins, inadequate feedback control, impaired response to TSH and TRH, cytokines-mediated actions, and selenium deficiency.(184, 185, 188, 191-215) Specific renal mechanisms have also been reported in patients with CKD and NTIS, including loss of thyroid hormones in the urine and effects of the reduced GFR.(216-218) Non-thyroidal illness syndrome in critically ill patients has been extensively reviewed(191, 194, 210, 219-226), but the syndrome has also been proven to happen with non-critical and/or chronic diseases.(215, 227-230) Changes in thyroid testing have also been reported after a significant stress, general anesthesia and/or a surgical procedure, and secondary to several drugs like glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs) among others.(10, 231-245) The magnitude of changes in thyroid hormones concentration correlates with the severity and/or duration of the disease.(223, 224, 246, 247) Importantly, the presence of NTIS has been associated with worsened outcomes and reduced survival both in human(187, 199, 215, 219, 220, 222, 225, 226, 229, 248-256) and veterinary medicine.(111, 122, 257-263) There is no clear evidence that patients with NTIS need thyroid hormone supplementation. However, it remains controversial in human medicine.(184, 185, 187, 215, 264)

B. Effects of NTIS on thyroid hormones and TSH

a) Humans

Typical changes seen in humans with NTIS are low fT3 and high rT3. Previously, NTIS was called "low T3 syndrome" for that reason. Decreased TT4 and fT4 occur in patients with severe or persistent NTIS.(183, 187) The TSH concentration can be decreased or normal, which differentiates NTIS from hypothyroidism. Serum TSH above normal is mainly seen in patients recovering from NTIS, and is transient.(187, 265, 266) The reported prevalence of NTIS in human patients admitted to ICU is between 44% and 70%, with 16-23% also showing a reduced T4.(199,

267-269) The prevalence of NTIS has been reported in specific critical illnesses, including sepsis (67%)(226), acute pancreatitis (64.7%)(225), COVID-19 (24-66%)(270-273), as well as many other. NTIS has also been reported in chronic diseases and non-critically ill patients, with a prevalence ranging from 20%-55%, with 15.5% having concurrently low T4 levels.(215, 227-230) As reported above, the presence of NTIS is associated with a negative outcome, with a direct correlation between the risk of death and the severity of decreases in T3 and T4.(187, 199, 215, 219, 220, 222, 225, 226, 229, 248-256, 274) Serum TSH alone is also considered a negative prognostic factor in patients with acute NTIS. A low TSH concentration is associated with short-term non-survival and severity of critical illness.(274-276) However, in several studies, the TSH concentration alone is not significantly associated with outcome, and is therefore less useful than T3 and T4 for this use in human patients.

b) Dogs

Similar to humans, dogs with NTIS will show a low TT3 with a raised rT3, as well as low TT4. Decreased fT4 concentration is less frequent (4.5-21%), mostly seen with severe illnesses (prevalence up to 70-85%).(190, 260, 261, 277, 278) The TSH concentration in dogs with NTIS is most of the time within the normal range.(190, 277) However, it can be decreased or elevated, with risk of misdiagnosing hypothyroidism in the latter case.(277-279) However, the combination of high TSH, low TT4 and low fT4 concentrations, consistent with a diagnosis of hypothyroidism, occurs only in 1-2% of dogs with NTIS.(277) Elevation of TSH is reported in 8-31% of dogs with NTIS, more often than in human medicine, and there is no association with the severity of the underlying disease.(277-280) On the other hand, low TSH concentration has been associated with non-survival and severity of the illness in a few studies, as seen in humans.(260, 281) The presence of NTIS has a negative prognostic value, associated with higher mortality and morbidity.(257-261, 263, 281, 282) Hormonal changes associated with NTIS are also transient, with resolution noted within 4 weeks of remission of the illness.(190, 283) The TT4 normalizes before the TT3, and an increase in TSH above the reference range can be noted during recovery.(190, 283)

c) Cats

Serum TT4 and TT3 are decreased in NTIS in cats, as seen in other species. A TT4 concentration below the lower limit of the reference range is seen in 21-23% of cats with NTIS, with a prevalence as high as 59% in cats suffering from severe illnesses.(111, 112, 122, 262) In a large study of almost 500 cats with NTIS, the diseases associated with lower TT4 levels included diabetes mellitus, hepatopathy, renal failure and systemic neoplasia.(111) Similar to humans and dogs, low TT4 and TT3 levels are also associated with non-survival, and the severity of the illness correlates with their degree of reduction.(111, 112, 122, 262, 263, 284) Indeed, a decreased TT4 has been shown to be a negative prognostic factor in most studies, which is not the case for other prognostic indicators, such as the systemic inflammatory response syndrome (SIRS) criteria and the level of acute phase proteins.(263, 284)

In comparison, fT4 is less predictable in the face of NTIS. In most cases, fT4 concentration will remain in the reference interval, but it will be decreased in 3-5% and increased in 6-12% of cases.(112, 122, 262) The fT4 concentration is not significantly different between NTIS and

controls, however cats with NTIS are more likely to have a high fT4 than healthy cats.(112, 122, 262) This is a major limiting factor, as it is impossible to differentiate a high fT4 from a cat with hyperthyroidism vs NTIS. As seen in humans and dogs, severe illnesses are associated with lower fT4 concentrations.(122, 262)

The behavior of TSH in cats with NTIS has only been evaluated in three studies, reporting a normal or decreased concentration (<0.03 ng/mL, based on the TSH-CLIA) in most cases. The opposite, an elevated TSH, is rarely seen in feline NTIS (2-3%).(101, 262, 285) Considering that 25-30% of healthy cats also have a suppressed TSH concentration, it is similar to what is seen with cats suffering from NTIS.(101, 127, 262) Indeed, levels of TSH do not differ between ill and healthy cats.(101, 262) An undetectable TSH concentration is seen in 31% of sick and 25% of healthy cats, which are not statistically different.(262) However, similar to humans and dogs with NTIS, a low TSH concentration is associated with the severity of the disease as well as short-term mortality.(262) Recently, a novel TSH assay (TSH-BAW) allowing a lower limit of detection of 0.008 ng/mL was evaluated in cats with variable thyroid status, including a group of 12 cats with chronic kidney disease without evidence of thyroid dysfunction. In this group, 17% had evidence of low TT4 concentration, and all had normal TSH values when measured with the TSH-BAW assay. When measured with the TSH-CLIA assay, only 1 cat had a suppressed TSH concentration.(101) In summary, TSH is not significantly affected by NTIS in cats based on the canine assay. However, further data is needed to conclude on the effect of NTIS on the TSH measured with the new feline-optimized assay.

Use of TSH in feline thyroid medicine disease

In addition to aiding in the diagnosis of FHT (see C. Diagnosis), TSH is also used for diagnosing hypothyroidism, with overt hypothyroidism being defined as a TT4 < 1.0 µg/dL and a TSH > 0.30 ng/mL, and subclinical hypothyroidism being described as a TT4 in the normal reference interval and a TSH > 0.30 ng/mL.(2, 171, 286) Naturally occurring hypothyroidism is rare in cats, and they mainly suffer from iatrogenic hypothyroidism (IH) following treatment of FHT.(2, 3) It can be a real problem following definitive therapy, including radioactive iodine and thyroidectomy. The burden of IH lies in its association with azotemia and reduced survival.(103, 175, 179) Unfortunately, the prevalence of IH post radioiodine treatment is relatively common and clinical signs are generally absent. Therefore, routine measurement of TT4 and TSH after radioiodine therapy is recommended to identify cats that develop IH post treatment (see D. Management, Radioiodine therapy).

A study involving 1,400 hyperthyroid cats revealed several parameters associated with an increased risk of developing IH after I^{131} therapy, including old age, female sex, bilateral disease with homogeneous distribution, and detectable TSH concentrations (>0.03 ng/mL).(102) The absence of TSH suppression seems to be the most predictive parameter, with odds ratio (OR) of 3.0 and 12.1 for development of subclinical and overt hypothyroidism, respectively.(102) Following this publication, it has been recommended to postpone I-131 treatment in cats with a detectable TSH concentration. This study was performed with the TSH-CLIA assay, and we do not know the performance of the TSH-BAW assay in this context. However, considering that 12% of cats have an unmeasurable TSH-CLIA (<0.03 ng/mL), but a normal TSH-BAW (≥0.01)(128),

the TSH-BAW assay could potentially help decrease the prevalence of IH after radioactive iodine therapy.

CHAPTER 2 – EVALUATION OF A FELINE-OPTIMIZED TSH ASSAY IN CATS WITH HYPERTHYROIDISM AND WITH NON-THYROIDAL ILLNESS

A. Introduction

Feline hyperthyroidism (FHT) is the most common endocrinopathy in senior cats(2, 33), and is being diagnosed in 10% of cats over 10 years of age.(69, 287)

Diagnosis of FHT is usually made by measuring serum total thyroxine (TT4) concentration. This method is quick, inexpensive, and highly sensitive. Up to 90% of hyperthyroid cats have a TT4 concentration above the reference interval.(38, 109, 110) However, 10-30% of them have a serum TT4 within the normal range.(38, 109, 110) This false negative result can be due to mild severity of disease (early hyperthyroidism) in conjunction with the natural fluctuation of the thyroid hormones in the body. However, it can also be secondary to concurrent non-thyroidal illness (NTI). Non-thyroid illnesses can lower the concentration of circulating T3 and T4, with the severity of decrease corresponding to the severity of the disease.(111, 112, 122, 262) Non-thyroidal illnesses are identified in 20-30% of hyperthyroid cats with a falsely lowered TT4.(109, 112)

When FHT is suspected but the serum TT4 concentration is not elevated, further tests are required to confirm the diagnosis. Diagnostic options include measurement of other thyroid hormones, stimulation and suppression tests, and thyroid scintigraphy. Measurement of serum free thyroxine (fT4) is of low utility, as 6.3% to 12% of cats with NTI will have a high fT4.(109, 122) Therefore, a fT4 above the reference interval cannot be used to diagnose FHT. Measurement of serum thyroid stimulating hormone (thyrotropin, TSH) in cats can also be problematic considering the absence of a feline assay. The chemiluminescent canine immunoassay (TSH-CLIA) has been validated in cats and is used to measure serum TSH concentrations in feline patients. The lowest limit of detection of the TSH-CLIA assay is 0.03 ng/mL, which unfortunately cannot differentiate between decreased and low normal values in cats, limiting its use to aid in the diagnosis of FHT. A suppressed TSH, consistent with hyperthyroidism, is seen in 98% of hyperthyroid cats, but also in 25-30% of euthyroid cats.(101, 127) This is an important limitation as it restricts the value of TSH-CLIA assay as a screening test for hyperthyroidism as done in people. Also, serum TSH is significantly less affected by NTI compared to other thyroid hormones, which is considerably advantageous in a population of cats with a falsely normal TT4. In the limited studies in cats, TSH concentrations are similar between ill and healthy subjects, and it is decreased only with severe concurrent illnesses.(199, 221, 262)

A feline-optimized assay using bulk acoustic wave (BAW) technology, the Truforma feline-optimized TSH assay by Zomedica (TSH-BAW), has become recently available with a lowest limit of detection of 0.008 ng/mL, and a low end of the normal reference range of 0.01 ng/mL.(128) Based on this data, 12% of healthy cats have an unmeasurable TSH-CLIA (<0.03 ng/mL), but normal TSH-BAW (≥0.01).(128) Therefore, TSH-BAW assay could better differentiate between normal and hyperthyroid cats, and potentially help with diagnosis of FHT when the TT4 is normal. The test has a high specificity (98.9%) and positive predictive value (86.9%) for diagnosis of FHT.(101) In this publication, the assay was also used on a small group of euthyroid cats with

CKD. Only one cat had an undetectable TSH-CLIA but normal TSH-BAW.(101) Other than this limited evaluation, the effect of NTI on the TSH-BAW assay has not been evaluated. Cats with hyperthyroidism are prone to comorbidities and signs of FHT can mimic other common feline diseases. It is important to assess its diagnostic utility for diagnosing FHT in the case of NTI.

The objectives of this prospective cross-sectional study are to 1) Compare serum TSH concentration using both the TSH-CLIA and TSH-BAW assays among hyperthyroid cats, cats with NTI, and healthy cats, and 2) Evaluate the sensitivity and specificity of the TSH-BAW for diagnosis of FHT. We hypothesize that 1) Hyperthyroid cats will have lower TSH-BAW concentrations compared to healthy and NTI cats, that 2) The TSH-BAW will identify normal TSH in euthyroid cats more often than the TSH-CLIA, and that 3) Cats with NTI will have similar TSH concentrations compared to healthy cats with both the TSH-BAW and TSH-CLIA assays.

B. Material and methods

This prospective cross-sectional study was performed on cats presenting to the Virginia-Maryland College of Veterinary Medicine (VMCVM) Veterinary Teaching Hospital (VTH) for medical care. It was approved by the Virginia Tech Institutional Animal Care and Use Committee (22-017). Written informed consent was obtained from each owner prior to participation in the study.

B.1 Case Selection

Client-owned and hospital staff-owned hyperthyroid cats, euthyroid cats with NTI and healthy cats were prospectively enrolled between January 2022 and July 2023. All cats underwent a complete physical examination, complete blood count (CBC), serum biochemistry, and thyroid hormones measurements (TT4 and TSH) by both immunoassays. Urinalysis (UA) was performed on most hyperthyroid cats and euthyroid cats with NTI when urine could be collected safely via cystocentesis or free-catch methodology (NOSORB litter, Catco Veterinary Products inc, Cape Coral, FL, USA).

Hyperthyroidism was confirmed by the presence of a high TT4 as well as consistent scintigraphy changes as previously described(173) in all hyperthyroid cats. Euthyroidism was confirmed by TT4 values within the reference range at presentation and at least 3 months later. Cats were diagnosed as healthy based on unremarkable physical examination and bloodwork (CBC, serum biochemistry, TT4 +/- UA) findings. Hyperthyroid cats were excluded if their history, physical examination, blood work and/or urinalysis revealed any abnormalities that could not be explained by FHT. Abnormalities considered consistent with FHT included low body condition score and muscle atrophy, tachycardia, heart murmur (unless reported before diagnosis of FHT), vomiting and diarrhea (unless reported before diagnosis of FHT), low creatinine, mild to moderate elevation of alanine transaminase (ALT), alkaline phosphatase (ALKP) and/or gamma-glutamyl transferase (GGT), diluted urine (USG <1.035), and proteinuria.(13) Euthyroid cats had to be 5 years of age or older for enrollment to mimic a feline hyperthyroid population.(13, 38-40) Cats that received medications known to alter thyroid hormone concentrations (reported in cats, dogs or humans) in the previous 14 days or general anesthesia in the past 48 hours were excluded.(10, 231-245)

B.2 TT4 and TSH Assays

Blood samples from all cats were collected, placed into plain non-additive tubes, and then centrifuged (1,500 X *g* for 10 to 15 minutes) within 1 hour after collection. The serum was immediately separated and stored at 4 °C until used for measurement of thyroid hormones. Measurement was performed on the same day unless exceptions.

Thyrotropin was measured on serum using a canine chemiluminescence assay (TSH-CLIA) with the Immulite 2000 (Siemens Healthineers; USA, Malvern, PA, USA) and the feline-optimized TSH assay (TSH-BAW) with the Truforma Point-of-Care (POC) Diagnostic Platform (Zomedica, Ann Harbor, MI, USA). Total thyroxine was measured on the same serum using the feline TT4 assay with the same Immulite 2000. Serum was manipulated by trained laboratory technicians for TT4 and TSH-CLIA, and by one of the investigators (C.B.) for the TSH-BAW assay as it is a POC device. It was performed according to the manufacturer's instructions, using the furnished material (pipettes and cartridges).(288)

The TSH-CLIA is a chemiluminescent immunometric assay with a lower limit of detection of 0.03 ng/mL. It has been validated for use in cats.(127) The lower limit of detection is also the low end of the reference interval, with an unmeasurable TSH (<0.03 ng/mL) considered abnormal. The TSH-BAW is a sandwich immunoassay using Bulk Acoustic Wave (BAW) technology. The BAW sensor measures shifts in radio frequency, resulting from antibody-analyte binding and accumulation onto the sensor surface. The lower limit of detection of the TSH-BAW assay is 0.008 ng/mL. The low end of the reference interval has been evaluated as 0.01 ng/mL.(101, 128)

B.3 Severity of NTI

Cats in the NTI group were further divided based on the severity of their illness. Group 1 included cats with diseases of mild severity, based on the following criteria: Asymptomatic or mild clinical signs that can be treated on an outpatient basis. Group 2 included cats with moderate to severe illness, which was defined based on the Systemic Inflammatory Response Syndrome (SIRS) criteria. In cats, it is determined by fulfillment of at least two of the following criteria: rectal temperature >103.5 ℉ or <100 ℉, heart rate >225 beats per minute (bpm) or <140 bpm, respiratory rate >40 breaths per minute, white blood cell count >19,500 cells/uL or <5,000 cells/uL, and band neutrophil fraction >5%.(289) Group 3 consisted of non-survivors.

B.3 Statistical analysis

Normal probability plots were inspected to assess the distribution properties of TSH-BAW and TSH-CLIA. Subsequently, data were summarized as median (minimum, maximum). Sensitivity and specificity of TSH-BAW and TSH-CLIA for detecting FHT were computed as simple binomial proportions with exact Clopper-Pearson 95% confidence intervals. Concentrations of TSH with both assays were compared using the Kruskal-Wallis test followed by Dunn's procedure for multiple comparisons. The proportion of cats with normal and subnormal TSH were compared between euthyroid groups and between NTI scores using Fisher's Exact test. *P*-values for 2-way comparisons were adjusted for multiple comparisons using Bonferonni's

procedure. Statistical significance was set to P <0.05. All analyses were performed using SAS version 9.4 (Cary, NC, USA).

C. Results

One hundred and two cats were enrolled in the study, with 37 hyperthyroid, 32 healthy and 33 NTI cats. The mean age and standard deviation of hyperthyroid, healthy and NTI cats was 11.7 +/- 2.2 yrs, 9.7 +/- 3.2 yrs, 11.2 +/- 4 yrs, respectively. The healthy euthyroid cats were significantly younger than the hyperthyroid cats (*P*=0.03). There were 77 Domestic Shorthair, 20 Domestic Longhair, 2 Siamese, and 1 each of the following breeds: Maincoon, Bengal, and Devon Rex. Fifty-six cats were spayed females, and the remaining 46 were castrated males. There was no difference between groups regarding the breed and sex distribution. In 4 hyperthyroid cats, a thyroid slip was not reported. Three euthyroid cats had a thyroid slip (2 healthy, 1 NTI). In 7 euthyroid cats (all healthy), the presence of a thyroid slip was not assessed by the attending clinician. The median concentrations of TT4 and TSH with both the TSH-CLIA and TSH-BAW assays are reported in table 1.

C.1 General performance of the TSH assays

The median TSH concentrations were significantly different between hyperthyroid and euthyroid cats (healthy and NTI cats) with both assays (P<0.002), and were not different between healthy and NTI cats (TSH-CLIA P=0.22, TSH-BAW P=0.87) (figure 1). The TSH-BAW assay had a sensitivity and specificity for the diagnosis of FHT of 78% (95% CI 62-90%) and 97% (84-100%), respectively. It had a positive predictive value (PPV) and negative predictive value (NPV) of 97% (83-100%) and 80% (64-91%), respectively. The sensitivity and specificity of the TSH-CLIA assay were 95% (81-99%) and 88% (72-97%), respectively. The PPV and NPV were 90% (76-99%) and 94% (79-99%), respectively. The proportion of cats with a suppressed TSH with the TSH-CLIA assay (<0.03 ng/mL) but normal with the TSH-BAW assay (≥0.01 ng/mL) was 19% (19 cats, including 11 euthyroid cats).

C.2 Hyperthyroid cats

The median TT4 concentrations of hyperthyroid cats were significantly higher than of euthyroid cats (healthy and NTI cats) (P<0.001) (table 1). With the TSH-CLIA assay, the TSH concentrations were suppressed (<0.03 ng/mL) in all hyperthyroid cats but one. With the TSH-BAW assay, the TSH concentrations were decreased (<0.01 ng/mL) in 29 (78.4%), and completely suppressed (<0.008 ng/mL) in 28 (75.7%) hyperthyroid cats. In this population, 8 cats (21.6%) had a suppressed TSH with the TSH-CLIA assay (<0.03 ng/mL) but normal with the TSH-BAW (≥0.01 ng/mL) (table 2). The median TT4 concentrations were not significantly different between hyperthyroid cats that had a normal TSH measured with the TSH-BAW (152.5 nmol/L, 55.1-212) vs. subnormal TSH (142 nmol/L, 69.4-453) (*P*=0.834) (figure 2).

C.3 Euthyroid cats

With the TSH-CLIA assay, the TSH concentrations were suppressed in 12 (18.5%) euthyroid cats, with 4 (12.5%) being healthy cats and 8 being (24.2%) cats with NTI. With the TSH-BAW assay, the TSH levels were suppressed in only 2 (3%) cats, 1 healthy and 1 with NTI (table 2). There was no difference in the median TSH concentration between healthy and NTI

euthyroid cats with both assays (TSH-CLIA P=0.29, TSH-BAW P=0.87) (figure 1). Six cats with NTI (18.2%) had a low TT4 concentration, with 5 (15.2%) that had an unreadable value. All healthy cats had a TT4 level within the reference interval. The median TT4 concentrations were not significantly different euthyroid healthy cats and cats with NTI (P=0.66) (table 1).

Cats with NTI were divided in three groups based on the severity of their illness. There were 15 cats, 14 cats and 4 cats in the groups 1, 2 and 3, respectively. Their NTI is reported in the table 3. The median TSH concentrations were not statistically different between each group with both assays (TSH-CLIA P=0.56, TSH-BAW P=0.70) (figure 3). With the TSH-CLIA, the TSH concentrations were suppressed in 2 (6.7%) cats in the group 1, 5 (35.7%) in the group 2, and 1 (25%) cat in the group 3. With the TSH-BAW assay, only 1 cat had a suppressed TSH, and was part of the group 2. The proportion of cats with a suppressed TSH was not different between groups and between assays, as reported in table 4a. However, when groups 2 and 3 were combined together, representing one group of cats with severe illnesses, the TSH concentrations (33.3%) were suppressed significantly more often with the TSH-CLIA assay (33.3%) than to the TSH-BAW assay (5.6%) (P<0.01) (table 4b). Similarly, when groups 1 and 2 were representing all the cats that survived, the proportion of cats with a decreased TSH (24.1%) was significantly higher with the TSH-CLIA assay (24.1%) compared to the TSH-BAW assay (3.4%) (P=0.03) (table 4c). Despite these differences between assays, no difference in proportions was observed between groups (mild vs severe diseases (TSH-CLIA P=0.24, TSH-BAW P=1.0), survivors vs non-survivors (TSH-CLIA P=1.0, TSH-BAW P=1.0).

D. Discussion

This report is one of the first studies evaluating a novel feline-optimized TSH assay, and is the first reporting its performance in various causes of NTI. There are only two other studies evaluating this assay.(101, 128)

For the use of the TSH-BAW assay for diagnosing FHT in cats that have an elevated TT4, we found a sensitivity and specificity of 78% and 97%, respectively. This result is similar to previously reported specificity of 98.9%.(101) As expected, this assay is highly specific, better than the canine assay (88% in our study, 70-85% in the literature).(2, 83, 101, 113, 127) This allows better differentiation between true hyperthyroid and euthyroid cats that have a TSH below 0.03 ng/mL. It also can identify euthyroid cats more often (97% of the time vs. 81.5% only with the TSH-CLIA). With such a high specificity, the TSH-BAW assay brings a significant diagnostic value to the diagnosis of FHT, especially when the TT4 is in the high normal of the reference interval.

However, the sensitivity of the TSH-BAW assay is lower than the TSH-CLIA based on our results. This is explained by the 21.6% of hyperthyroid cats that had a normal TSH-BAW concentration (over 0.01 ng/mL). As these cats still had a TSH value below 0.03 ng/mL (and therefore a suppressed TSH-CLIA), the sensitivity of the canine assay ended up being significantly higher at 95%. All of our hyperthyroid cats had a TSH concentration below 0.014 ng/mL when measured by the TSH-BAW assay. Serum TSH below this threshold was rarely seen

in euthyroid cats (2 healthy, 4 with NTI). Based on our result, we can conclude that FHT is unlikely if the TSH is over 0.014 ng/mL.

When compared with the study by Peterson et al.(101), our sensitivity results are somewhat similar. In that study, the sensitivity of the TSH-BAW assay when combined with TT4 measurement was 84.6%, compared to 90.5% when the TSH was used alone for the diagnosis. (101) Our sensitivity of 79.9% is more comparable to the sensitivity of 84.6%, where all cats in the hyperthyroid group had to have a high TT4 for inclusion in our study. The small difference in sensitivity between the two studies could relate to study design for inclusion criteria in the hyperthyroid group and possible intrinsic differences in population.

In a recent study evaluating TSH-BAW in cats that divided hyperthyroid cats by severity, it was shown that cats with subclinical and mild hyperthyroidism were more likely to have a TSH concentration within the reference range. Indeed, 13.7% of those cats (including 27.5% with subclinical hyperthyroidism) did not have a decreased TSH(101), which is similar to our results. This has also been reported with the TSH-CLIA assay, with early/mild forms of the disease being associated with detectable levels of TSH.(102, 127). This suggests that the hypothalamus-pituitary-thyroid axis has not yet been suppressed by the excessive amount of thyroid hormones in circulation. However, some cats with severe hyperthyroidism still have a normal TSH concentration, therefore other factors are likely contributing. Based on TT4 concentrations, we did not find a significant difference between the cats that had a suppressed TSH and those that did not (see figure 2). Considering that the degree of TT4 elevation is known to correlate directly with the severity of hyperthyroidism(101), mild forms of the disease are unlikely the only reason for a detectable or normal TSH in our population of cats.

Other than for diagnosis of FHT, the TSH concentration can have additional utilities with hyperthyroid cats. For example, it has been shown to be an important prognostic factor for response to treatment with I^{131}.(102) Indeed, a detectable TSH-CLIA is associated with development of iatrogenic hypothyroidism (IH) with odd ratios of 3.0 and 12.1 for subclinical and overt hypothyroidism, respectively. This can be explained by the fact that TSH directly stimulates the normal thyroid tissue, which should be inactive in the case of hyperthyroidism due to the negative feedback created by elevated thyroid hormone levels. Because of the TSH in circulation, those normal thyroid cells are functional and therefore uptake the radioactive iodine, leading to their destruction. Based on aforementioned study and the burden of IH in cats that undergo I^{131} treatment, the TSH should be measured prior to considering this therapy. Our results show that 21.6% of hyperthyroid cats with normal TSH levels are being missed by the TSH-CLIA assay. This suggests that the TSH-BAW assay could help reduce the prevalence of IH, however further research is needed to make such a conclusion. Indeed, no studies have used the TSH-BAW assay yet to evaluate this specific prognostic factor.

In our study, the median TSH concentration of euthyroid cats did not differ with both assays, whether they were healthy or suffering from a NTI. This supports the thought that the TSH is less affected by NTI than other thyroid hormones in cats, as it has been demonstrated previously.(101, 262) However, it is not completely immune to the effect of NTI, as one study

found that a suppressed TSH (using the TSH-CLIA assay) was associated with severe illnesses as well as a higher risk of mortality.(262) In that study, the TSH concentration did not differ between groups either, however having a subnormal TSH value was associated with a negative prognosis. Our results showed a trend in the same direction for the TSH-CLIA assay, however we did not reach statistical significance, likely due to the small number of cats with NTI of different severity. In our study, the proportion of cats with a suppressed TSH was twice as high in the NTI group (24.2%) compared to the healthy controls (12.5%) with the TSH-CLIA assay. Also, an undetectable TSH was more prevalent in cats suffering from illnesses of greater severity (6.7% of cats with mild diseases compared to 33.3% of cats with moderate to severe illnesses). These results suggest that the serum TSH concentrations measured with the TSH-CLIA assay could decrease in the face of NTI, especially if the illness is severe.

Interestingly, this trend was not found with the TSH-BAW assay, and there were significantly less cats with a suppressed TSH compared to the TSH-CLIA assay. This suggests that the TSH-BAW assay is significantly less affected by NTI than the TSH-CLIA assay. Considering that both healthy and NTI groups have similar results with the TSH- BAW, the superiority of this assay might not be only explained by the fact that it can detect a normal TSH more often. As our results did not show a significant effect of NTI on TSH concentrations using the TSH-BAW assay, this lack of difference could be due to type II error. Further study with a larger population of ill cats with different disease severity is likely needed to further assess the effects of NTI on the TSH-BAW assay. As of right now, we can suggest that the TSH when measured with the TSH-BAW assay does not seem to be significantly affected by NTI, or that the effect is too mild to be seen with our results. This is also consistent with the only other study evaluating the TSH-BAW assay with euthyroid cats with NTI, which again involved a small group of only 12 cats with CKD.(101)

This study contains several limitations. Our NTI group most likely lacked power to fully assess the effect of severe diseases (and mortality) on the TSH-BAW. In addition, categorization of illnesses by severity is strongly subjective. Unfortunately, this has been and will remain a major limitation in veterinary medicine research because of how hard it is to define strict criteria for such diverse clinical presentations. Objectivity was attempted by using the already known SIRS criteria, however they are known to be imprecise and lacking specificity (even if these limitations seem to be less dramatic in cats).(289) Nevertheless, this subjectivity makes it more difficult to compare different studies together in regards to the effect of disease severity on TSH concentration. Another limitation is that thyroid scintigraphy was not used to confirm euthyroidism. As this currently is the best test available to evaluate thyroid function, this test involves specialized staff and equipment, quarantined isolation due to radioactivity, use of sedation in some cats, and high costs. Considering that TT4 is highly sensitive(2, 13, 38, 40, 101, 109) and the natural progression of FHT, we elected to define euthyroidism based on a normal TT4 both at inclusion and at least 3 months later. By repeating TT4 measurement, we could detect most hyperthyroid cats that were subclinical or ill at time of inclusion. Unfortunately, some cats could not be rechecked (4 healthy and 19 NTI cats), either due to loss to follow-up or death of the patient. Therefore, we may have included a small number of hyperthyroid cats in the euthyroid groups. Lastly, we did not include subclinical hyperthyroid cats in our study. This population consists of about 40% of hyperthyroid

cats with a high normal TT4 concentration(33, 110), and could therefore benefit specifically from TSH measurement as part of diagnosis of FHT. Subclinical hyperthyroid cats are also known to have higher TSH levels, which has been demonstrated by Peterson et al. with the TSH-BAW assay.(101) It would have been ideal to confirm their results by evaluating this population in our study.

CHAPTER 3 – CONCLUSION

In conclusion, the novel feline-optimized TSH assay (Truforma, Zomedica) has a high specificity for diagnosis of feline hyperthyroidism, and identifies normal TSH in healthy cats more often. It does not seem to be significantly affected by NTI, and is a better test for confirming hyperthyroidism compared to the canine assay (Immulite 2000, Siemens) in this regard. It is therefore a useful tool for the diagnosis of FHT, especially in cats with high normal TT4 concentrations and concurrent diseases. However, a normal TSH should not be used to rule out the disease. That being said, based on our data, a TSH > 0.014 ng/ml makes FHT unlikely.

As it is a novel assay, there is still so much to learn about it. For example, if it is affected by severe illnesses in a study with a large number of cats, or if it can also predict mortality in euthyroid sick cats like the canine assay does. And for hyperthyroid cats precisely, it could be of such importance clinically if it can help anticipate the development of iatrogenic hypothyroidism following radioactive iodine therapy. Indeed, the next step is to evaluate if a normal and/or a detectable TSH-BAW is associated with this adverse effect. A large population of cats treated with I^{131} would be needed for this kind of study, and a multicenter approach might be ideal.

REFERENCES

1. A. Rijnberk HSK. Clinical Endocrinology of Dogs and Cats. Second Edition ed. Hannover, Germany: Schlütersche Verlagsgesellschaft mbH & Co.; 2010. 338 p.
2. Feldman E NR, Reusch C, Scott-Moncrieff J, Behrend E. Canine & feline endocrinology. 4th edition ed: Saunders; 2015. 688 p.
3. Feldman EC, Fracassi F, Peterson ME. Feline Endocrinology: Edra S.p.A.; 2019.
4. Hall JE, Hall ME. Guyton and Hall textbook of medical physiology e-Book: Elsevier Health Sciences; 2020.
5. Feldt-Rasmussen U, Effraimidis G, Klose M. The hypothalamus-pituitary-thyroid (HPT)-axis and its role in physiology and pathophysiology of other hypothalamus-pituitary functions. Mol Cell Endocrinol. 2021;525:111173.
6. Foster DJ, Thoday KL, Beckett GJ. Thyroid hormone deiodination in the domestic cat. J Mol Endocrinol. 2000;24(1):119-26.
7. Kuiper GG, Wassen F, Klootwijk W, Van Toor H, Kaptein E, Visser TJ. Molecular basis for the substrate selectivity of cat type I iodothyronine deiodinase. Endocrinology. 2003;144(12):5411-21.
8. Mariotti S, Beck-Peccoz P. Physiology of the Hypothalamic-Pituitary-Thyroid Axis. Endotext. South Dartmouth (MA): MDText.com, Inc.
Copyright © 2000-2024, MDText.com, Inc.; 2016.
9. Peterson ME, Graves TK, Cavanagh I. Serum thyroid hormone concentrations fluctuate in cats with hyperthyroidism. J Vet Intern Med. 1987;1(3):142-6.
10. Daminet S, Ferguson DC. Influence of drugs on thyroid function in dogs. J Vet Intern Med. 2003;17(4):463-72.
11. Salvatore D, Davies TF, Schlumberger M, Hay ID, Larsen PR. Thyroid Physiology and Diagnostic Evaluation of Patients with Thyroid Disorders. In: Elsevier/Saunders, editor. Williams textbook of endocrinology. Ed 12 ed. Philadelphia2011.
12. Sterling K, Brenner MA. Thyroid hormone action: effect of triiodothyronine on mitochondrial adenine nucleotide translocase in vivo and in vitro. Metabolism. 1995;44(2):193-9.
13. Peterson ME, Kintzer PP, Cavanagh PG, Fox PR, Ferguson DC, Johnson GF, et al. Feline hyperthyroidism: pretreatment clinical and laboratory evaluation of 131 cases. J Am Vet Med Assoc. 1983;183(1):103-10.
14. Naan EC, Kirpensteijn J, Kooistra HS, Peeters ME. Results of Thyroidectomy in 101 Cats with Hyperthyroidism. Veterinary Surgery. 2006;35(3):287-93.
15. Peterson ME, Becker DV. Radionuclide Thyroid Imaging in 135 Cats with Hyperthyroidism. Veterinary Radiology. 1984;25(1):23-7.
16. Harvey AM, Hibbert A, Barrett EL, Day MJ, Quiggin AV, Brannan RM, et al. Scintigraphic findings in 120 hyperthyroid cats. Journal of Feline Medicine and Surgery. 2009;11(2):96-106.
17. Lucke V. An Histological Study of Thyroid Abnormalities in the Domestic Cat. Journal of Small Animal Practice. 1964;5:351-8.
18. Turrel JM, Feldman EC, Nelson RW, Cain GR. Thyroid carcinoma causing hyperthyroidism in cats: 14 cases (1981-1986). J Am Vet Med Assoc. 1988;193(3):359-64.
19. Peterson ME, Broome MR. Thyroid scintigraphy findings in 2096 cats with hyperthyroidism. Veterinary Radiology & Ultrasound. 2015;56(1):84-95.
20. Peterson ME. ANIMAL MODELS OF DISEASE: Feline hyperthyroidism: an animal model for toxic nodular goiter. Journal of Endocrinology. 2014;223(2):T97-T114.
21. Beck-Peccoz P, Persani L, Lania A. Thyrotropin-Secreting Pituitary Adenomas. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.
Copyright © 2000-2024, MDText.com, Inc.; 2000.

22. Beck-Peccoz P, Persani L, Mannavola D, Campi I. Pituitary tumours: TSH-secreting adenomas. Best Pract Res Clin Endocrinol Metab. 2009;23(5):597-606.
23. Köhler B, Stengel C, Neiger R. Dietary hyperthyroidism in dogs. J Small Anim Pract. 2012;53(3):182-4.
24. Shadwick SR, Ridgway MD, Kubier A. Thyrotoxicosis in a dog induced by the consumption of feces from a levothyroxine-supplemented housemate. Can Vet J. 2013;54(10):987-9.
25. Singer PA. Thyroiditis. Acute, subacute, and chronic. Med Clin North Am. 1991;75(1):61-77.
26. Kennedy RL, Thoday KL. Autoantibodies in feline hyperthyroidism. Res Vet Sci. 1988;45(3):300-6.
27. Kennedy R, Thoday K. Lack of thyroid stimulatory activity in the serum of hyperthyroid cats. Autoimmunity. 1989;3:317-8.
28. Peterson M, Livingston P, Brown R. Lack of circulating thyroid stimulating immunoglobulins in cats with hyperthyroidism. Veterinary Immunology and Immunopathology. 1987;16:277-82.
29. Nguyen LQ, Arseven OK, Gerber H, Stein BS, Jameson JL, Kopp P. Cloning of the cat TSH receptor and evidence against an autoimmune etiology of feline hyperthyroidism. Endocrinology. 2002;143(2):395-402.
30. Peter HJ, Gerber H, Studer H, Becker DV, Peterson ME. Autonomy of growth and of iodine metabolism in hyperthyroid feline goiters transplanted onto nude mice. J Clin Invest. 1987;80(2):491-8.
31. Peter HJ, Gerber H, Studer H, Peterson ME, Becker DV, Groscurth P. Autonomous growth and function of cultured thyroid follicles from cats with spontaneous hyperthyroidism. Thyroid. 1991;1(4):331-8.
32. Ward CR, Achenbach SE, Holt D, Peterson ME, Meinkoth JL. Thyrotropin-stimulated DNA synthesis and thyroglobulin expression in normal and hyperthyroid feline thyrocytes in monolayer culture. Thyroid. 2005;15(2):114-20.
33. Ettinger SJ, Feldman EC, Côté É. Textbook of Veterinary Internal Medicine-Inkling E-Book: Elsevier health sciences; 2016.
34. Watson SG, Radford AD, Kipar A, Ibarrola P, Blackwood L. Somatic mutations of the thyroid-stimulating hormone receptor gene in feline hyperthyroidism: parallels with human hyperthyroidism. J Endocrinol. 2005;186(3):523-37.
35. Ward CR, Windham WR, Dise D. Evaluation of activation of G proteins in response to thyroid stimulating hormone in thyroid gland cells from euthyroid and hyperthyroid cats. Am J Vet Res. 2010;71(6):643-8.
36. Hammer KB, Holt DE, Ward CR. Altered expression of G proteins in thyroid gland adenomas obtained from hyperthyroid cats. Am J Vet Res. 2000;61(8):874-9.
37. Merryman JI, Buckles EL, Bowers G, Neilsen NR. Overexpression of c-Ras in hyperplasia and adenomas of the feline thyroid gland: an immunohistochemical analysis of 34 cases. Vet Pathol. 1999;36(2):117-24.
38. Broussard JD, Peterson ME, Fox PR. Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. Journal of the American Veterinary Medical Association. 1995;206(3):302-5.
39. Edinboro CH, Scott-Moncrieff JC, Janovitz E, Thacker HL, Glickman LT. Epidemiologic study of relationships between consumption of commercial canned food and risk of hyperthyroidism in cats. Journal of the American Veterinary Medical Association. 2004;224(6):879-86.
40. Thoday KL, Mooney CT. Historical, clinical and laboratory features of 126 hyperthyroid cats. Vet Rec. 1992;131(12):257-64.
41. Griffin MA, Solomon DH. Hyperthyroidism in the elderly. J Am Geriatr Soc. 1986;34(12):887-92.

42. Mooradian AD. Asymptomatic hyperthyroidism in older adults: is it a distinct clinical and laboratory entity? Drugs Aging. 2008;25(5):371-80.
43. Bond BR, Fox PR, Peterson ME, Skavaril RV. Echocardiographic findings in 103 cats with hyperthyroidism. J Am Vet Med Assoc. 1988;192(11):1546-9.
44. Peterson ME, Keene B, Ferguson DC, Pipers FS. Electrocardiographic findings in 45 cats with hyperthyroidism. J Am Vet Med Assoc. 1982;180(8):934-7.
45. Connolly DJ, Guitian J, Boswood A, Neiger R. Serum troponin I levels in hyperthyroid cats before and after treatment with radioactive iodine. J Feline Med Surg. 2005;7(5):289-300.
46. Fox PR, Peterson ME, Broussard JD. Electrocardiographic and radiographic changes in cats with hyperthyroidism: comparison of populations evaluated during 1992-1993 vs. 1979-1982. Journal of the American Animal Hospital Association. 1999;35(1):27-31.
47. Stepien R, Rapoport G, Henik R, Sartor L, Wenholz L. Effect of measurement method on blood pressure findings in cats before and after therapy for hyperthyroidism. J Vet Intern Med. 2003;17:754.
48. Morrow L, Adams VJ, Elliott J, Syme HM. Hypertension in hyperthyroid cats: prevalence. incidence and predictors of its development2009.
49. Syme H, Elliott J. The prevalence of hypertension in hyperthyroid cats at diagnosis and following treatment. J Vet Intern Med. 2003;17(1):754-5.
50. Kobayashi DL, Peterson ME, Graves TK, Lesser M, Nichols CE. Hypertension in cats with chronic renal failure or hyperthyroidism. J Vet Intern Med. 1990;4(2):58-62.
51. Syme HM. Cardiovascular and renal manifestations of hyperthyroidism. Veterinary Clinics of North America: Small Animal Practice. 2007;37(4):723-43.
52. van der Woerdt A, Peterson ME. Prevalence of ocular abnormalities in cats with hyperthyroidism. J Vet Intern Med. 2000;14(2):202-3.
53. Peterson ME, Castellano CA, Rishniw M. Evaluation of Body Weight, Body Condition, and Muscle Condition in Cats with Hyperthyroidism. J Vet Intern Med. 2016;30(6):1780-9.
54. JP L. Feline renal failure: questions, answers, questions. Comp Cont Educ Pract Vet. 1992;14:127-52.
55. Milner RJ, Channell CD, Levy JK, Schaer M. Survival times for cats with hyperthyroidism treated with iodine 131, methimazole, or both: 167 cases (1996-2003). J Am Vet Med Assoc. 2006;228(4):559-63.
56. Williams TL, Peak KJ, Brodbelt D, Elliott J, Syme HM. Survival and the development of azotemia after treatment of hyperthyroid cats. J Vet Intern Med. 2010;24(4):863-9.
57. Boag AK, Neiger R, Slater L, Stevens KB, Haller M, Church DB. Changes in the glomerular filtration rate of 27 cats with hyperthyroidism after treatment with radioactive iodine. Vet Rec. 2007;161(21):711-5.
58. Graves T, Olivier N, Nachreiner R, Kruger J, Walshaw R, Stickle R. Changes in renal function associated with treatment of hyperthyroidism in cats. American Journal of Veterinary Research. 1994;55(12):1745-9.
59. Adams WH, Daniel GB, Legendre AM, Gompf RE, Grove CA. Changes in renal function in cats following treatment of hyperthyroidism using 131I. Vet Radiol Ultrasound. 1997;38(3):231-8.
60. Becker TJ, Graves TK, Kruger JM, Braselton WE, Nachreiner RF. Effects of methimazole on renal function in cats with hyperthyroidism. J Am Anim Hosp Assoc. 2000;36(3):215-23.
61. Feeney DA, Jessen CR, Weichselbaum RC. Paired Pre-and Post-treatment Serum Biochemical Parameters and Thyroxine Concentrations in a Cohort of Ninety Seven Radioiodine-treated Hyperthyroid Cats. International Journal of Applied Research in Veterinary Medicine. 2011;9(1).
62. van Hoek I, Lefebvre HP, Peremans K, Meyer E, Croubels S, Vandermeulen E, et al. Short- and long-term follow-up of glomerular and tubular renal markers of kidney function in hyperthyroid cats after treatment with radioiodine. Domest Anim Endocrinol. 2009;36(1):45-56.

63. Peterson ME, Rishniw M. Urine concentrating ability in cats with hyperthyroidism: Influence of radioiodine treatment, masked azotemia, and iatrogenic hypothyroidism. J Vet Intern Med. 2023;37(6):2039-51.
64. Peterson M, Johnson JG, Andrews LK. Spontaneous hyperthyroidism in the cat. Proceedings of the American College of Veterinary Internal Medicine; Seattle, Washington1979.
65. Holzworth J, Theran P, Carpenter JL, Harpster NK, Todoroff RJ. Hyperthyroidism in the cat: ten cases. J Am Vet Med Assoc. 1980;176(4):345-53.
66. Jones BR, Johnstone AC. Hyperthyroidism in an aged cat. New Zealand veterinary journal. 1981;29 5:70-2.
67. Peterson ME, Ward CR. Etiopathologic findings of hyperthyroidism in cats. Vet Clin North Am Small Anim Pract. 2007;37(4):633-45, v.
68. McLean JL, Lobetti RG, Schoeman JP. Worldwide prevalence and risk factors for feline hyperthyroidism: A review. J S Afr Vet Assoc. 2014;85(1):1097.
69. Peterson M. Hyperthyroidism in cats: what's causing this epidemic of thyroid disease and can we prevent it? J Feline Med Surg. 2012;14(11):804-18.
70. Scarlett JM, Moise NS, Rayl J. Feline hyperthyroidism: A descriptive and case-control study. Preventive veterinary medicine. 1988;6(4):295-309.
71. Jones B, Engdahl JN, Weiss J. Are persistent organic pollutants important in the etiology of feline hyperthyroidism? A review. Acta Vet Scand. 2019;61(1):45.
72. Sassnau R. Epidemiological investigation on the prevalence of feline hyperthyroidism in an urban population in Germany. Tierärztliche Praxis Ausgabe K, Kleintiere/Heimtiere. 2006;34:450-+.
73. Wakeling J, Melian C, Font A, Elliott J, Syme H, editors. Evidence for differing incidences of feline hyperthyroidism in London UK and Spain. Proceedings of the 15th ECVIM-CA Congress; 2005.
74. De Wet CS, Mooney CT, Thompson PN, Schoeman JP. Prevalence of and risk factors for feline hyperthyroidism in Hong Kong. J Feline Med Surg. 2009;11(4):315-21.
75. Miyamoto T. Prevalence of feline hyperthyroidism in Osaka and the Chugoku region. JOURNAL-JAPAN VETERINARY MEDICAL ASSOCIATION. 2002;55(5):289-92.
76. Köhler I, Ballhausen BD, Stockhaus C, Hartmann K, Wehner A. Prevalence of and risk factors for feline hyperthyroidism among a clinic population in Southern Germany. Tierarztl Prax Ausg K Kleintiere Heimtiere. 2016;44(3):149-57.
77. Stephens MJ, O'Neill DG, Church DB, McGreevy PD, Thomson PC, Brodbelt DC. Feline hyperthyroidism reported in primary-care veterinary practices in England: prevalence, associated factors and spatial distribution. Vet Rec. 2014;175(18):458.
78. Bree L, Gallagher BA, Shiel RE, Mooney CT. Prevalence and risk factors for hyperthyroidism in Irish cats from the greater Dublin area. Ir Vet J. 2018;71:2.
79. Kass PH, Peterson ME, Levy J, James K, Becker DV, Cowgill LD. Evaluation of Environmental, Nutritional, and Host Factors in Cats with Hyperthyroidism. 1999;13(4):323.
80. Olczak J, Jones B, Pfeiffer D, Squires R, Morris R, Markwell P. Multivariate analysis of risk factors for feline hyperthyroidism in New Zealand. New Zealand Veterinary Journal. 2005;53(1):53-8.
81. Wakeling J, Everard A, Brodbelt D, Elliott J, Syme H. Risk factors for feline hyperthyroidism in the UK. Journal of Small Animal Practice. 2009;50(8):406-14.
82. Martin KM, Rossing MA, Ryland LM, DiGiacomo RF, Freitag WA. Evaluation of dietary and environmental risk factors for hyperthyroidism in cats. Journal of the American Veterinary Medical Association. 2000;217(6):853-6.
83. Wakeling J, Elliott J, Syme H. Evaluation of Predictors for the Diagnosis of Hyperthyroidism in Cats. Journal of Veterinary Internal Medicine. 2011;25(5):1057-65.
84. Laurberg P, Pedersen KM, Vestergaard H, Sigurdsson G. High incidence of multinodular toxic goitre in the elderly population in a low iodine intake area vs. high incidence of Graves'

disease in the young in a high iodine intake area: comparative surveys of thyrotoxicosis epidemiology in East-Jutland Denmark and Iceland. J Intern Med. 1991;229(5):415-20.
85. Pedersen I, Knudsen N, Jørgensen T, Perrild H, Ovesen L, Laurberg P. Large differences in incidences of overt hyper- and hypothyroidism associated with a small difference in iodine intake: a prospective comparative register-based population survey. J Clin Endocrinol Metab. 2002;87(10):4462-9.
86. Roti E, Uberti ED. Iodine excess and hyperthyroidism. Thyroid. 2001;11(5):493-500.
87. Edinboro CH, Scott-Moncrieff JC, Glickman LT. Feline hyperthyroidism: potential relationship with iodine supplement requirements of commercial cat foods. J Feline Med Surg. 2010;12(9):672-9.
88. Edinboro CH, Pearce EN, Pino S, Braverman LE. Iodine concentration in commercial cat foods from three regions of the USA, 2008–2009. Journal of Feline Medicine and Surgery. 2013;15(8):717-24.
89. Johnson L, Ford H, Tarttelin Ma, Feek C. Iodine content of commercially-prepared cat foods. New Zealand Veterinary Journal. 1992;40(1):18-20.
90. Hooper SE, Backus R, Amelon S. Effects of dietary selenium and moisture on the physical activity and thyroid axis of cats. J Anim Physiol Anim Nutr (Berl). 2018;102(2):495-504.
91. Sabatino BR, Rohrbach BW, Armstrong PJ, Kirk CA. Amino acid, iodine, selenium, and coat color status among hyperthyroid, Siamese, and age-matched control cats. J Vet Intern Med. 2013;27(5):1049-55.
92. Foster DJ, Thoday KL, Arthur JR, Nicol F, Beatty JA, Svendsen CK, et al. Selenium status of cats in four regions of the world and comparison with reported incidence of hyperthyroidism in cats in those regions. Am J Vet Res. 2001;62(6):934-7.
93. Doerge DR, Sheehan DM. Goitrogenic and estrogenic activity of soy isoflavones. Environ Health Perspect. 2002;110 Suppl 3(Suppl 3):349-53.
94. Kang JH, Kondo F. Determination of bisphenol A in canned pet foods. Res Vet Sci. 2002;73(2):177-82.
95. Schecter A, Malik N, Haffner D, Smith S, Harris TR, Paepke O, et al. Bisphenol A (BPA) in U.S. food. Environ Sci Technol. 2010;44(24):9425-30.
96. Dye JA, Venier M, Zhu L, Ward CR, Hites RA, Birnbaum LS. Elevated PBDE levels in pet cats: sentinels for humans? Environ Sci Technol. 2007;41(18):6350-6.
97. Walter KM, Lin YP, Kass PH, Puschner B. Association of Polybrominated Diphenyl Ethers (PBDEs) and Polychlorinated Biphenyls (PCBs) with Hyperthyroidism in Domestic Felines, Sentinels for Thyroid Hormone Disruption. BMC Vet Res. 2017;13(1):120.
98. Bahn Chair RS, Burch HB, Cooper DS, Garber JR, Greenlee MC, Klein I, et al. Hyperthyroidism and other causes of thyrotoxicosis: management guidelines of the American Thyroid Association and American Association of Clinical Endocrinologists. Thyroid. 2011;21(6):593-646.
99. Santos Palacios S, Pascual-Corrales E, Galofre JC. Management of subclinical hyperthyroidism. Int J Endocrinol Metab. 2012;10(2):490-6.
100. Wakeling J, Smith K, Scase T, Kirkby R, Elliott J, Syme H. Subclinical hyperthyroidism in cats: a spontaneous model of subclinical toxic nodular goiter in humans? Thyroid. 2007;17(12):1201-9.
101. Peterson ME, Dougherty E, Rishniw M. Evaluation of a novel, sensitive thyroid-stimulating hormone assay as a diagnostic test for thyroid disease in cats. Am J Vet Res. 2024;85(5).
102. Peterson ME, Rishniw M. Predicting outcomes in hyperthyroid cats treated with radioiodine. J Vet Intern Med. 2022;36(1):49-58.
103. Peterson ME, Rishniw M. A dosing algorithm for individualized radioiodine treatment of cats with hyperthyroidism. J Vet Intern Med. 2021;35(5):2140-51.

104. Boretti FS, Sieber-Ruckstuhl NS, Gerber B, Laluha P, Baumgartner C, Lutz H, et al. Thyroid enlargement and its relationship to clinicopathological parameters and T(4) status in suspected hyperthyroid cats. J Feline Med Surg. 2009;11(4):286-92.
105. Chaitman J HR, Senz R, et al. Thyroid adenomatous hyperplasia in euthyroid cats. J Vet Intern Med. 1999.
106. Norsworthy GD, Adams VJ, McElhaney MR, Milios JA. Relationship between semi-quantitative thyroid palpation and total thyroxine concentration in cats with and without hyperthyroidism. J Feline Med Surg. 2002;4(3):139-43.
107. Norsworthy GD, Adams VJ, McElhaney MR, Milios JA. Palpable thyroid and parathyroid nodules in asymptomatic cats. J Feline Med Surg. 2002;4(3):145-51.
108. Ferguson D FR. Goiter in apparently euthyroid cats. In: Saunders E, editor. Consultations in Feline Internal Medicine. 5th ed ed. St. Louis2006.
109. Peterson ME, Melián C, Nichols R. Measurement of serum concentrations of free thyroxine, total thyroxine, and total triiodothyronine in cats with hyperthyroidism and cats with nonthyroidal disease. Journal of the American Veterinary Medical Association. 2001;218(4):529-36.
110. Peterson ME. Diagnostic tests for hyperthyroidism in cats. Clin Tech Small Anim Pract. 2006;21(1):2-9.
111. Peterson ME, Gamble DA. Effect of nonthyroidal illness on serum thyroxine concentrations in cats: 494 cases (1988). J Am Vet Med Assoc. 1990;197(9):1203-8.
112. McLoughlin M, DiBartola S, Birchard S, Day D. Influence of systemic nonthyroidal illness on serum concentration of thyroxine in hyperthyroid cats. Journal (USA). 1993.
113. Peterson ME. More than just T4: diagnostic testing for hyperthyroidism in cats. Journal of feline medicine and surgery. 2013;15(9):765-77.
114. Gerber H, Peter H, Ferguson DC, Peterson ME. Etiopathology of feline toxic nodular goiter. Veterinary clinics of north America: Small animal practice. 1994;24(3):541-65.
115. Kemppainen RJ, Birchfield JR. Measurement of total thyroxine concentration in serum from dogs and cats by use of various methods. Am J Vet Res. 2006;67(2):259-65.
116. Singh AK, Jiang Y, White T, Spassova D. Validation of nonradioactive chemiluminescent immunoassay methods for the analysis of thyroxine and cortisol in blood samples obtained from dogs, cats, and horses. Journal of Veterinary Diagnostic Investigation. 1997;9(3):261-8.
117. Lurye JC, Behrend EN, Kemppainen RJ. Evaluation of an in-house enzyme-linked immunosorbent assay for quantitative measurement of serum total thyroxine concentration in dogs and cats. Journal of the American Veterinary Medical Association. 2002;221(2):243-9.
118. Horney BS, MacKenzie AL, Burton SA, Olexson DW, Mitton KL, Coty WA, et al. Evaluation of an automated, homogeneous enzyme immunoassay for serum thyroxine measurement in dog and cat serum. Vet Clin Pathol. 1999;28(1):20-8.
119. Ferguson D. Free thyroid hormone measurements in the diagnosis of thyroid disease. Kirk's current veterinary therapy XII Philadelphia: WB Saunders Co. 1995:360-4.
120. Kaptein EM. Clinical application of free thyroxine determinations. Clinics in laboratory medicine. 1993;13(3):653-72.
121. Nachreiner R, Refsal K. Collection, storage and transport of samples. BSAVA Manual of Canine and Feline Endocrinology (ed 3) Gloucester, UK, British Small Animal Veterinary Association. 2004:1-5.
122. Mooney CT, Little CJ, Macrae AW. Effect of illness not associated with the thyroid gland on serum total and free thyroxine concentrations in cats. J Am Vet Med Assoc. 1996;208(12):2004-8.
123. Rasmussen SH, Andersen HH, Kjelgaard-Hansen M. Combined assessment of serum free and total T4 in a general clinical setting seemingly has limited potential in improving diagnostic accuracy of thyroid dysfunction in dogs and cats. Vet Clin Pathol. 2014;43(1):1-3.

124. Thienpont LM, Van Uytfanghe K, Poppe K, Velkeniers B. Determination of free thyroid hormones. Best Practice & Research Clinical Endocrinology & Metabolism. 2013;27(5):689-700.
125. Stammeleer L, Buresova E, Stock E, Feenstra L, Vandermeulen E, Duchateau L, et al. Comparison of free thyroxine measurement by chemiluminescence and equilibrium dialysis following (131)I therapy in hyperthyroid cats. J Feline Med Surg. 2020;22(12):1114-20.
126. Schachter S, Nelson RW, Scott-Moncrieff C, Ferguson DC, Montgomery T, Feldman EC, et al. Comparison of serum-free thyroxine concentrations determined by standard equilibrium dialysis, modified equilibrium dialysis, and 5 radioimmunoassays in dogs. Journal of veterinary internal medicine. 2004;18(3):259-64.
127. Peterson ME, Guterl JN, Nichols R, Rishniw M. Evaluation of Serum Thyroid-Stimulating Hormone Concentration as a Diagnostic Test for Hyperthyroidism in Cats. Journal of Veterinary Internal Medicine. 2015;29(5):1327-34.
128. Wood AM BB, Moore IM, Peterson ME. Determination of serum TSH using novel, feline-optimized TSH immunoassay: New diagnostic test for hyperthyroid cats? Journal of Veterinary Internal Medicine. 2021.
129. Länge K. Bulk and surface acoustic wave sensor arrays for multi-analyte detection: A review. Sensors. 2019;19(24):5382.
130. Fischer SK, Williams K, Harmon I, Bothwell B, Xu H, Capio E, et al. Evaluation of two point of care technologies for measuring monoclonal antibody therapeutic-A concentrations in blood. Bioanalysis. 2020;12(20):1449-58.
131. Peterson ME, Graves TK, Gamble DA. Triiodothyronine (T3) Suppression Test. Journal of Veterinary Internal Medicine. 1990;4(5):233-8.
132. Peterson ME, Graves TK, Gamble DA. Triiodothyronine (T3) suppression test: an aid in the diagnosis of mild hyperthyroidism in cats. Journal of Veterinary Internal Medicine. 1990;4(5):233-8.
133. Refsal KR, Nachreiner RF, Stein BE, Currigan CE, Zendel AN, Thacker EL. Use of the triiodothyronine suppression test for diagnosis of hyperthyroidism in ill cats that have serum concentration of iodothyronines within normal range. Journal of the American Veterinary Medical Association. 1991;199(11):1594-601.
134. Peterson ME, Broussard JD, Gamble DA. Use of the thyrotropin releasing hormone stimulation test to diagnose mild hyperthyroidism in cats. Journal of Veterinary Internal Medicine. 1994;8(4):279-86.
135. Graves TK, Peterson ME. Diagnostic tests for feline hyperthyroidism. Veterinary Clinics of North America: Small Animal Practice. 1994;24(3):567-76.
136. Beleslin DB, Jovanović-Mićić D, Samardzić R, Terzić B. Studies on thyrotropin-releasing hormone-induced micturition in cats. J Pharm Pharmacol. 1987;39(6):474-6.
137. Beleslin DB, Jovanović-Micić D, Samardzić R, Terzić B. Studies of thyrotropin-releasing hormone (TRH)-induced defecation in cats. Pharmacol Biochem Behav. 1987;26(3):639-41.
138. Beleslin DB, Jovanovic-Micic D, Tomic-Beleslin N. Nature of salivation produced by thyrotropin-releasing hormone (TRH). Brain Res Bull. 1987;18(3):463-5.
139. Holtman JR, Jr., Buller AL, Hamosh P, Gillis RA. Central respiratory stimulation produced by thyrotropin-releasing hormone in the cat. Peptides. 1986;7(2):207-12.
140. Mooney C, Thoday K, Doxey D. Serum thyroxine and triiodothyronine responses of hyperthyroid cats to thyrotropin. American journal of veterinary research. 1996;57(7):987-91.
141. Tomsa K, Glaus TM, Kacl GM, Pospischil A, Reusch CE. Thyrotropin-releasing hormone stimulation test to assess thyroid function in severely sick cats. Journal of veterinary internal medicine. 2001;15(2):89-93.
142. Daniel GB, Sharp DS, Nieckarz JA, Adams W. Quantitative thyroid scintigraphy as a predictor of serum thyroxin concentration in normal and hyperthyroid cats. Veterinary Radiology & Ultrasound. 2002;43(4):374-82.

143. Mooney CT, Thoday KL, Nicoll JJ, Doxey DL. Qualitative and quantitative thyroid imaging in feline hyperthyroidism using technetium-99m as pertechnetate. Veterinary Radiology & Ultrasound. 1992;33(5):313-20.
144. Peterson ME, Kintzer PP, Hurvitz AI. Methimazole treatment of 262 cats with hyperthyroidism. J Vet Intern Med. 1988;2(3):150-7.
145. Manna D, Roy G, Mugesh G. Antithyroid drugs and their analogues: synthesis, structure, and mechanism of action. Acc Chem Res. 2013;46(11):2706-15.
146. Taurog A. The mechanism of action of the thioureylene antithyroid drugs. Endocrinology. 1976;98(4):1031-46.
147. Aucoin DP, Peterson ME, Hurvitz AI, Drayer DE, Lahita RG, Quimby FW, et al. Propylthiouracil-induced immune-mediated disease in the cat. J Pharmacol Exp Ther. 1985;234(1):13-8.
148. Peterson ME, Hurvitz AI, Leib MS, Cavanagh PG, Dutton RE. Propylthiouracil-associated hemolytic anemia, thrombocytopenia, and antinuclear antibodies in cats with hyperthyroidism. J Am Vet Med Assoc. 1984;184(7):806-8.
149. Caney SM. An online survey to determine owner experiences and opinions on the management of their hyperthyroid cats using oral anti-thyroid medications. J Feline Med Surg. 2013;15(6):494-502.
150. Peterson ME. Hyperthyroidism in Cats: Considering the Impact of Treatment Modality on Quality of Life for Cats and Their Owners. Vet Clin North Am Small Anim Pract. 2020;50(5):1065-84.
151. Peterson ME, Broome MR, Rishniw M. Prevalence and degree of thyroid pathology in hyperthyroid cats increases with disease duration: a cross-sectional analysis of 2096 cats referred for radioiodine therapy. J Feline Med Surg. 2016;18(2):92-103.
152. Daminet S, Kooistra H, Fracassi F, Graham P, Hibbert A, Lloret A, et al. Best practice for the pharmacological management of hyperthyroid cats with antithyroid drugs. Journal of small animal practice. 2014;55(1):4-13.
153. Lécuyer M, Prini S, Dunn ME, Doucet MY. Clinical efficacy and safety of transdermal methimazole in the treatment of feline hyperthyroidism. Can Vet J. 2006;47(2):131-5.
154. Sartor LL, Trepanier LA, Kroll MM, Rodan I, Challoner L. Efficacy and safety of transdermal methimazole in the treatment of cats with hyperthyroidism. J Vet Intern Med. 2004;18(5):651-5.
155. Grossi G, Zoia A, Palagiano P, Leoni N, Bubini-Regini F, Malerba E, et al. Iodine-restricted food versus pharmacological therapy in the management of feline hyperthyroidism: A controlled trial in 34 cats. Open Vet J. 2019;9(3):196-204.
156. Hui TY, Bruyette DS, Moore GE, Scott-Moncrieff JC. Effect of Feeding an Iodine-Restricted Diet in Cats with Spontaneous Hyperthyroidism. J Vet Intern Med. 2015;29(4):1063-8.
157. van der Kooij M, Bečvářová I, Meyer HP, Teske E, Kooistra HS. Effects of an iodine-restricted food on client-owned cats with hyperthyroidism. J Feline Med Surg. 2014;16(6):491-8.
158. Fritsch D, Allen T, Dodd C, Wedekind K, Sixby K. A Restricted Iodine Food Reduces Circulating Thyroxine Concentrations in Cats with Hyperthyroidism. International Journal of Applied Research in Veterinary Medicine. 2014;12:24-32.
159. Scott-Moncrieff JC, Heng HG, Weng HY, Dimeo D, Jones MD. Effect of a Limited Iodine Diet on Iodine Uptake by Thyroid Glands in Hyperthyroid Cats. J Vet Intern Med. 2015;29(5):1322-6.
160. Vaske H. Assessment of renal function in hyperthyroid cats managed with a controlled iodine diet: Kansas State University; 2015.
161. Loftus JP, DeRosa S, Struble AM, Randolph JF, Wakshlag JJ. One-year study evaluating efficacy of an iodine-restricted diet for the treatment of moderate-to-severe hyperthyroidism in cats. Veterinary Medicine: Research and Reports. 2019:9-16.

162. Loftus J, Peterson M. Treatment of hyperthyroidism: diet. W: Feldman EC, Fracassi F, Peterson ME (eds): Feline Endocrinology Edra SpA, Milano. 2019:255-66.
163. Peterson ME. Radioiodine Treatment of Hyperthyroidism. Clinical Techniques in Small Animal Practice. 2006;21(1):34-9.
164. Peterson ME, Becker DV. Radioiodine treatment of 524 cats with hyperthyroidism. J Am Vet Med Assoc. 1995;207(11):1422-8.
165. Peterson M, Xifra M, Broome M. Treatment of hyperthyroidism: radioiodine. Feline Endocrinology Milan: EDRA. 2019:227-54.
166. Vaske HH, Schermerhorn T, Armbrust L, Grauer GF. Diagnosis and management of feline hyperthyroidism: current perspectives. Veterinary Medicine: Research and Reports. 2014;5:85-96.
167. Hibbert A, Gruffydd-Jones T, Barrett EL, Day MJ, Harvey AM. Feline thyroid carcinoma: diagnosis and response to high-dose radioactive iodine treatment. 2009.
168. Guptill L, Catharine J, Scott-Moncrieff R, Janovitz EB, Blevins WE, Yohn SE, et al. Response to high-dose radioactive iodine administration in cats with thyroid carcinoma that had previously undergone surgery. Journal of the American Veterinary Medical Association. 1995;207(8):1055-8.
169. Puille M, Puille N, Neiger R, Bauer R. Radioiodine treatment of feline hyperthyroidism: radiation safety of contact persons. TIERAERZTLICHE PRAXIS AUSGABE KLEINTIERE HEIMTIERE. 2005;33(4):291-5.
170. Boland LA, Murray JK, Bovens CP, Hibbert A. A survey of owners' perceptions and experiences of radioiodine treatment of feline hyperthyroidism in the UK. Journal of Feline Medicine and Surgery. 2014;16(8):663-70.
171. Lucy JM, Peterson ME, Randolph JF, Scrivani PV, Rishniw M, Davignon DL, et al. Efficacy of Low-dose (2 millicurie) versus Standard-dose (4 millicurie) Radioiodine Treatment for Cats with Mild-to-Moderate Hyperthyroidism. J Vet Intern Med. 2017;31(2):326-34.
172. Matos J, Lutz B, Grandt LM, Meneses F, Schweizer-Gorgas D, Francey T, et al. Outcome of radioiodine therapy for feline hyperthyroidism: Fixed dose versus individualized dose based on a clinical scoring system. Open Vet J. 2022;12(2):231-41.
173. Morré WA, Panciera DL, Daniel GB, Monroe WE, Werre S. Investigation of a novel variable dosing protocol for radioiodine treatment of feline hyperthyroidism. J Vet Intern Med. 2018;32(6):1856-63.
174. Mullowney D, Chang YM, Glanemann B, Syme HM. Treatment failure in hyperthyroid cats after radioiodine (I-131) injection. J Vet Intern Med. 2021;35(4):1688-96.
175. Fernandez Y, Puig J, Powell R, Seth M. Prevalence of iatrogenic hypothyroidism in hyperthyroid cats treated with radioiodine using an individualised scoring system. J Feline Med Surg. 2019;21(12):1149-56.
176. Peterson M, Varela F, Rishniw M. Radioiodine treatment of cats with hyperthyroidism: evaluation of a novel algorithm for individual dose calculation based on thyroid scintigraphy, serum thyroid hormone concentrations, and thyroid uptake of radioiodine. J Vet Intern Med. 2018;32:2139-40.
177. Peterson M. Diagnosis and Management of Iatrogenic Hypothyroidism. In: Sciences EH, editor. Consultations in Feline Internal Medicine. 6. St. Louis, MO2016. p. 260-9.
178. Peterson M, Rishniw M. Hyperthyroid cats develop transient or persistent subclinical hypothyroidism after successful radioiodine treatment. J Vet Intern Med. 2017;31:222.
179. Williams TL, Elliott J, Syme HM. Association of iatrogenic hypothyroidism with azotemia and reduced survival time in cats treated for hyperthyroidism. J Vet Intern Med. 2010;24(5):1086-92.
180. Flanders J. Treatment of hyperthyroidism: surgical thyroidectomy. W: Feldman EC, Fracassi F, Peterson ME (eds): Feline Endocrinology Edra SpA, Milano. 2019:211-26.

181. Flanders J, Harvey H, Erb H. Feline Thyroidectomy A Comparison of Postoperative Hypocalcemia Associated with Three Different Surgical Techniques. Veterinary Surgery. 1987;16(5):362-6.
182. Welches C, Scavelli T, Matthiensen D, Peterson M. Occurrence of problems after three techniques of bilateral thyroidectomy in cats. Veterinary Surgery. 1989;18(5):392-6.
183. Adler SM, Wartofsky L. The Nonthyroidal Illness Syndrome. Endocrinology and Metabolism Clinics of North America. 2007;36(3):657-72.
184. Wajner SM, Maia AL. New Insights toward the Acute Non-Thyroidal Illness Syndrome. Front Endocrinol (Lausanne). 2012;3:8.
185. Langouche L, Jacobs A, Van den Berghe G. Nonthyroidal Illness Syndrome Across the Ages. Journal of the Endocrine Society. 2019;3(12):2313-25.
186. Docter R, Krenning EP, de Jong M, Hennemann G. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. Clin Endocrinol (Oxf). 1993;39(5):499-518.
187. DeGroot LJ. The Non-Thyroidal Illness Syndrome. In: Feingold KR, Anawalt B, Blackman MR, Boyce A, Chrousos G, Corpas E, et al., editors. Endotext. South Dartmouth (MA): MDText.com, Inc.
Copyright © 2000-2024, MDText.com, Inc.; 2000.
188. Warner MH, Beckett GJ. Mechanisms behind the non-thyroidal illness syndrome: an update. J Endocrinol. 2010;205(1):1-13.
189. Hamblin PS, Dyer SA, Mohr VS, Le Grand BA, Lim CF, Tuxen DV, et al. Relationship between thyrotropin and thyroxine changes during recovery from severe hypothyroxinemia of critical illness. J Clin Endocrinol Metab. 1986;62(4):717-22.
190. Bolton TA, Panciera DL, Voudren CD, Crawford-Jennings MI. Thyroid function tests during nonthyroidal illness syndrome and recovery in acutely ill dogs. J Vet Intern Med. 2024;38(1):111-22.
191. Burger A, Nicod P, Suter P, Vallotton MB, Vagenakis P, Braverman L. Reduced active thyroid hormone levels in acute illness. Lancet. 1976;1(7961):653-5.
192. Kwakkel J, van Beeren HC, Ackermans MT, Platvoet-Ter Schiphorst MC, Fliers E, Wiersinga WM, et al. Skeletal muscle deiodinase type 2 regulation during illness in mice. J Endocrinol. 2009;203(2):263-70.
193. Maia AL, Kim BW, Huang SA, Harney JW, Larsen PR. Type 2 iodothyronine deiodinase is the major source of plasma T3 in euthyroid humans. J Clin Invest. 2005;115(9):2524-33.
194. Peeters RP, Wouters PJ, Kaptein E, van Toor H, Visser TJ, Van den Berghe G. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. J Clin Endocrinol Metab. 2003;88(7):3202-11.
195. Boelen A, Kwakkel J, Alkemade A, Renckens R, Kaptein E, Kuiper G, et al. Induction of type 3 deiodinase activity in inflammatory cells of mice with chronic local inflammation. Endocrinology. 2005;146(12):5128-34.
196. Rodriguez-Perez A, Palos-Paz F, Kaptein E, Visser TJ, Dominguez-Gerpe L, Alvarez-Escudero J, et al. Identification of molecular mechanisms related to nonthyroidal illness syndrome in skeletal muscle and adipose tissue from patients with septic shock. Clin Endocrinol (Oxf). 2008;68(5):821-7.
197. Simonides WS, Mulcahey MA, Redout EM, Muller A, Zuidwijk MJ, Visser TJ, et al. Hypoxia-inducible factor induces local thyroid hormone inactivation during hypoxic-ischemic disease in rats. J Clin Invest. 2008;118(3):975-83.
198. Beigneux AP, Moser AH, Shigenaga JK, Grunfeld C, Feingold KR. Sick euthyroid syndrome is associated with decreased TR expression and DNA binding in mouse liver. Am J Physiol Endocrinol Metab. 2003;284(1):E228-36.

199. Plikat K, Langgartner J, Buettner R, Bollheimer LC, Woenckhaus U, Schölmerich J, et al. Frequency and outcome of patients with nonthyroidal illness syndrome in a medical intensive care unit. Metabolism. 2007;56(2):239-44.
200. Kwakkel J, Chassande O, van Beeren HC, Fliers E, Wiersinga WM, Boelen A. Thyroid hormone receptor {alpha} modulates lipopolysaccharide-induced changes in peripheral thyroid hormone metabolism. Endocrinology. 2010;151(4):1959-69.
201. Boelen A, Maas MA, Lowik CW, Platvoet MC, Wiersinga WM. Induced illness in interleukin-6 (IL-6) knock-out mice: a causal role of IL-6 in the development of the low 3,5,3'-triiodothyronine syndrome. Endocrinology. 1996;137(12):5250-4.
202. Kwakkel J, Wiersinga WM, Boelen A. Differential involvement of nuclear factor-kappaB and activator protein-1 pathways in the interleukin-1beta-mediated decrease of deiodinase type 1 and thyroid hormone receptor beta1 mRNA. J Endocrinol. 2006;189(1):37-44.
203. Kwakkel J, Wiersinga WM, Boelen A. Interleukin-1beta modulates endogenous thyroid hormone receptor alpha gene transcription in liver cells. J Endocrinol. 2007;194(2):257-65.
204. Boelen A, Platvoet-ter Schiphorst MC, Bakker O, Wiersinga WM. The role of cytokines in the lipopolysaccharide-induced sick euthyroid syndrome in mice. J Endocrinol. 1995;146(3):475-83.
205. Corssmit EP, Heyligenberg R, Endert E, Sauerwein HP, Romijn JA. Acute effects of interferon-alpha administration on thyroid hormone metabolism in healthy men. J Clin Endocrinol Metab. 1995;80(11):3140-4.
206. Boelen A, Schiphorst MC, Wiersinga WM. Relationship between serum 3,5,3'-triiodothyronine and serum interleukin-8, interleukin-10 or interferon gamma in patients with nonthyroidal illness. J Endocrinol Invest. 1996;19(7):480-3.
207. van der Poll T, Van Zee KJ, Endert E, Coyle SM, Stiles DM, Pribble JP, et al. Interleukin-1 receptor blockade does not affect endotoxin-induced changes in plasma thyroid hormone and thyrotropin concentrations in man. J Clin Endocrinol Metab. 1995;80(4):1341-6.
208. de Vries EM, Fliers E, Boelen A. The molecular basis of the non-thyroidal illness syndrome. J Endocrinol. 2015;225(3):R67-81.
209. Boelen A, Kwakkel J, Wiersinga WM, Fliers E. Chronic local inflammation in mice results in decreased TRH and type 3 deiodinase mRNA expression in the hypothalamic paraventricular nucleus independently of diminished food intake. J Endocrinol. 2006;191(3):707-14.
210. Mebis L, Debaveye Y, Ellger B, Derde S, Ververs EJ, Langouche L, et al. Changes in the central component of the hypothalamus-pituitary-thyroid axis in a rabbit model of prolonged critical illness. Crit Care. 2009;13(5):R147.
211. Boelen A, Kwakkel J, Thijssen-Timmer DC, Alkemade A, Fliers E, Wiersinga WM. Simultaneous changes in central and peripheral components of the hypothalamus-pituitary-thyroid axis in lipopolysaccharide-induced acute illness in mice. J Endocrinol. 2004;182(2):315-23.
212. Fekete C, Gereben B, Doleschall M, Harney JW, Dora JM, Bianco AC, et al. Lipopolysaccharide induces type 2 iodothyronine deiodinase in the mediobasal hypothalamus: implications for the nonthyroidal illness syndrome. Endocrinology. 2004;145(4):1649-55.
213. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. J Clin Endocrinol Metab. 1997;82(12):4032-6.
214. Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. Crit Care Med. 1998;26(9):1536-44.
215. Pappa TA, Vagenakis AG, Alevizaki M. The nonthyroidal illness syndrome in the non-critically ill patient. Eur J Clin Invest. 2011;41(2):212-20.
216. Basu G, Mohapatra A. Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab. 2012;16(2):204-13.

217. Iglesias P, Bajo MA, Selgas R, Díez JJ. Thyroid dysfunction and kidney disease: An update. Rev Endocr Metab Disord. 2017;18(1):131-44.
218. Song SH, Kwak IS, Lee DW, Kang YH, Seong EY, Park JS. The prevalence of low triiodothyronine according to the stage of chronic kidney disease in subjects with a normal thyroid-stimulating hormone. Nephrol Dial Transplant. 2009;24(5):1534-8.
219. Slag MF, Morley JE, Elson MK, Crowson TW, Nuttall FQ, Shafer RB. Hypothyroxinemia in critically ill patients as a predictor of high mortality. Jama. 1981;245(1):43-5.
220. Tognini S, Marchini F, Dardano A, Polini A, Ferdeghini M, Castiglioni M, et al. Non-thyroidal illness syndrome and short-term survival in a hospitalised older population. Age Ageing. 2010;39(1):46-50.
221. Lee WK, Hwang S, Kim D, Lee SG, Jeong S, Seol MY, et al. Distinct Features of Nonthyroidal Illness in Critically Ill Patients With Infectious Diseases. Medicine (Baltimore). 2016;95(14):e3346.
222. Vidart J, Jaskulski P, Kunzler AL, Marschner RA, Ferreira de Azeredo da Silva A, Wajner SM. Non-thyroidal illness syndrome predicts outcome in adult critically ill patients: a systematic review and meta-analysis. Endocr Connect. 2022;11(2).
223. Peeters RP, Wouters PJ, van Toor H, Kaptein E, Visser TJ, Van den Berghe G. Serum 3,3',5'-triiodothyronine (rT3) and 3,5,3'-triiodothyronine/rT3 are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. J Clin Endocrinol Metab. 2005;90(8):4559-65.
224. Fliers E, Bianco AC, Langouche L, Boelen A. Thyroid function in critically ill patients. Lancet Diabetes Endocrinol. 2015;3(10):816-25.
225. Qu C, Duan Z, Xiao X, Wei M, Gao K, Yu X, et al. Nonthyroidal illness syndrome in acute pancreatitis patients: an 8-year cohort study. BMC Gastroenterology. 2022;22(1):40.
226. Padhi R, Kabi S, Panda BN, Jagati S. Prognostic significance of nonthyroidal illness syndrome in critically ill adult patients with sepsis. Int J Crit Illn Inj Sci. 2018;8(3):165-72.
227. Karadag F, Ozcan H, Karul AB, Yilmaz M, Cildag O. Correlates of non-thyroidal illness syndrome in chronic obstructive pulmonary disease. Respiratory Medicine. 2007;101(7):1439-46.
228. Gumus A, Ozyurt S, Ozcelik N, Kara BY. Prevalence of non-thyroidal illness syndrome in COPD exacerbation and effect of hypoxaemia and hypercapnia on thyroid functions. Clin Respir J. 2020;14(9):806-12.
229. Zargar AH, Ganie MA, Masoodi SR, Laway BA, Bashir MI, Wani AI, et al. Prevalence and pattern of sick euthyroid syndrome in acute and chronic non-thyroidal illness--its relationship with severity and outcome of the disorder. J Assoc Physicians India. 2004;52:27-31.
230. Kaptein EM, Kaptein JS, Chang EI, Egodage PM, Nicoloff JT, Massry SG. Thyroxine transfer and distribution in critical nonthyroidal illnesses, chronic renal failure, and chronic ethanol abuse. J Clin Endocrinol Metab. 1987;65(4):606-16.
231. Burr WA, Black EG, Griffiths RS, Hoffenberg R. Serum triiodothyronine and reverse triiodothyronine concentrations after surgical operation. Lancet. 1975;2(7948):1277-9.
232. Burger A, Dinichert D, Nicod P, Jenny M, Lemarchand-Béraud T, Vallotton MB. Effect of amiodarone on serum triiodothyronine, reverse triiodothyronine, thyroxin, and thyrotropin. A drug influencing peripheral metabolism of thyroid hormones. J Clin Invest. 1976;58(2):255-9.
233. Chopra IJ, Williams DE, Orgiazzi J, Solomon DH. Opposite effects of dexamethasone on serum concentrations of 3,3',5'-triiodothyronine (reverse T3) and 3,3'5-triiodothyronine (T3). J Clin Endocrinol Metab. 1975;41(5):911-20.
234. Eber O, Buchinger W, Lindner W, Lind P, Rath M, Klima G, et al. The effect of D- versus L-propranolol in the treatment of hyperthyroidism. Clin Endocrinol (Oxf). 1990;32(3):363-72.
235. van der Heijden JT, Krenning EP, van Toor H, Hennemann G, Docter R. Three-compartmental analysis of effects of D-propranolol on thyroid hormone kinetics. Am J Physiol. 1988;255(1 Pt 1):E80-6.

236. Verhoeven RP, Visser TJ, Doctor R, Hennemann G, Schalekamp MA. Plasma thyroxine, 3,3',5-triiodothyronine and 3,3',5'-triiodothyronine during beta-adrenergic blockade in hyperthyroidism. J Clin Endocrinol Metab. 1977;44(5):1002-5.
237. Wood MA, Panciera DL, Berry SH, Monroe WE, Refsal KR. Influence of isoflurane general anesthesia or anesthesia and surgery on thyroid function tests in dogs. J Vet Intern Med. 2009;23(1):7-15.
238. Sauvé F, Paradis M, Refsal KR, Moreau M, Beauchamp G, Dupuis J. Effects of oral administration of meloxicam, carprofen, and a nutraceutical on thyroid function in dogs with osteoarthritis. Can Vet J. 2003;44(6):474-9.
239. Liu PM, Zhang XM, Wu W, Li JM, Tang Y. Comparison of cardiac electrophysiologic effects of experimental hypothyroidism and chronic oral amiodarone administration in dogs. Chin Med J (Engl). 1994;107(5):375-9.
240. Panciera DL, Refsal KR, Sennello KA, Ward DL. Effects of deracoxib and aspirin on serum concentrations of thyroxine, 3,5,3'-triiodothyronine, free thyroxine, and thyroid-stimulating hormone in healthy dogs. Am J Vet Res. 2006;67(4):599-603.
241. Gulikers KP, Panciera DL. Evaluation of the effects of clomipramine on canine thyroid function tests. J Vet Intern Med. 2003;17(1):44-9.
242. Harper A, Blackwood L, Mason S. Investigation of thyroid function in dogs treated with the tyrosine kinase inhibitor toceranib. Vet Comp Oncol. 2020;18(3):433-7.
243. Gamstedt A, Järnerot G, Kågedal B, Söderholm B. Corticosteroids and thyroid function. Different effects on plasma volume, thyroid hormones and thyroid hormone-binding proteins after oral and intravenous administration. Acta Med Scand. 1979;205(5):379-83.
244. Elmahdi B, Hassan M, El-Bahr S. Effect of prednisolone on thyroid and gonadotrophic hormones secretion in male domestic rabbits. Thyroid Research and Practice. 2016;13:136.
245. Jensen J, Nolan G, Jubiz W. The effect of prednisone on serum thyrotropin, thyroxine and triiodothyronine concentrations in hypothyroid patients. Journal of Endocrinological Investigation. 1978;1(2):171-3.
246. Wehmann RE, Gregerman RI, Burns WH, Saral R, Santos GW. Suppression of thyrotropin in the low-thyroxine state of severe nonthyroidal illness. N Engl J Med. 1985;312(9):546-52.
247. van Zyl E, Leisewitz AL, Atkinson BK, Goddard A, Rautenbach Y, Thompson PN, et al. Serial changes in the concentrations of cortisol and thyroid hormones in Beagle dogs infected with Babesia rossi. Ticks Tick Borne Dis. 2023;14(2):102107.
248. Miao X, Fu X, Liu H, Gu Z, Li C, Wang K, et al. Analysis of clinical features and 7-year all-cause mortality in older male patients with non-thyroidal illness syndrome on general wards. Eur Geriatr Med. 2023;14(2):363-71.
249. Maldonado LS, Murata GH, Hershman JM, Braunstein GD. Do thyroid function tests independently predict survival in the critically ill? Thyroid. 1992;2(2):119-23.
250. Iervasi G, Pingitore A, Landi P, Raciti M, Ripoli A, Scarlattini M, et al. Low-T3 syndrome: a strong prognostic predictor of death in patients with heart disease. Circulation. 2003;107(5):708-13.
251. Scoscia E, Baglioni S, Eslami A, Iervasi G, Monti S, Todisco T. Low triiodothyronine (T3) state: a predictor of outcome in respiratory failure? Results of a clinical pilot study. Eur J Endocrinol. 2004;151(5):557-60.
252. Alevizaki M, Synetou M, Xynos K, Pappa T, Vemmos KN. Low triiodothyronine: a strong predictor of outcome in acute stroke patients. Eur J Clin Invest. 2007;37(8):651-7.
253. Forestier E, Vinzio S, Sapin R, Schlienger JL, Goichot B. Increased reverse triiodothyronine is associated with shorter survival in independently-living elderly: the Alsanut study. Eur J Endocrinol. 2009;160(2):207-14.
254. Ataoğlu HE, Ahbab S, Serez MK, Yamak M, Kayaş D, Canbaz ET, et al. Prognostic significance of high free T4 and low free T3 levels in non-thyroidal illness syndrome. European Journal of Internal Medicine. 2018;57:91-5.

255. Gutch M, Kumar S, Gupta KK. Prognostic Value of Thyroid Profile in Critical Care Condition. Indian J Endocrinol Metab. 2018;22(3):387-91.
256. El-Ella SSA, El-Mekkawy MS, El-Dihemey MA. Prevalence and prognostic value of non-thyroidal illness syndrome among critically ill children. An Pediatr (Engl Ed). 2019;90(4):237-43.
257. Mooney CT, Shiel RE, Dixon RM. Thyroid hormone abnormalities and outcome in dogs with non-thyroidal illness. J Small Anim Pract. 2008;49(1):11-6.
258. Giunti M, Troia R, Battilani M, Giardino L, Dondi F, Andreani G, et al. Retrospective evaluation of circulating thyroid hormones in critically ill dogs with systemic inflammatory response syndrome. J Vet Sci. 2017;18(4):471-7.
259. Schoeman JP, Goddard A, Herrtage ME. Serum cortisol and thyroxine concentrations as predictors of death in critically ill puppies with parvoviral diarrhea. J Am Vet Med Assoc. 2007;231(10):1534-9.
260. Schoeman JP, Herrtage ME. Serum thyrotropin, thyroxine and free thyroxine concentrations as predictors of mortality in critically ill puppies with parvovirus infection: a model for human paediatric critical illness? Microbes Infect. 2008;10(2):203-7.
261. Oikonomidis IL, Theodorou K, Papaioannou E, Xenoulis PG, Adamama-Moraitou KK, Steiner JM, et al. Serial measurement of thyroid hormones in hospitalised dogs with canine parvoviral enteritis: Incidence of non-thyroidal illness syndrome and its association with outcome and systemic inflammatory response syndrome. Vet J. 2021;274:105715.
262. Peterson ME, Davignon DL, Shaw N, Dougherty E, Rishniw M, Randolph JF. Serum thyroxine and thyrotropin concentrations decrease with severity of nonthyroidal illness in cats and predict 30-day survival outcome. J Vet Intern Med. 2020;34(6):2276-86.
263. Petini M, Drigo M, Zoia A. Prognostic value of systemic inflammatory response syndrome and serum concentrations of acute phase proteins, cholesterol, and total thyroxine in cats with panleukopenia. J Vet Intern Med. 2020;34(2):719-24.
264. Sciacchitano S, Capalbo C, Napoli C, Anibaldi P, Salvati V, De Vitis C, et al. Nonthyroidal Illness Syndrome: To Treat or Not to Treat? Have We Answered the Question? A Review of Metanalyses. Front Endocrinol (Lausanne). 2022;13:850328.
265. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. J Clin Endocrinol Metab. 1986;63(1):1-8.
266. Bacci V, Schussler GC, Kaplan TB. The relationship between serum triiodothyronine and thyrotropin during systemic illness. J Clin Endocrinol Metab. 1982;54(6):1229-35.
267. Chopra IJ. Clinical review 86: Euthyroid sick syndrome: is it a misnomer? J Clin Endocrinol Metab. 1997;82(2):329-34.
268. Kaplan MM, Larsen PR, Crantz FR, Dzau VJ, Rossing TH, Haddow JE. Prevalence of abnormal thyroid function test results in patients with acute medical illnesses. Am J Med. 1982;72(1):9-16.
269. Bermudez F, Surks MI, Oppenheimer JH. High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. The Journal of Clinical Endocrinology & Metabolism. 1975;41(1):27-40.
270. Baldelli R, Nicastri E, Petrosillo N, Marchioni L, Gubbiotti A, Sperduti I, et al. Thyroid dysfunction in COVID-19 patients. Journal of Endocrinological Investigation. 2021;44(12):2735-9.
271. Okoye C, Niccolai F, Rogani S, Lemmi B, Peta U, Del Vecchio S, et al. Is non-thyroidal illness syndrome (NTIS) a clinical predictor of COVID-19 mortality in critically ill oldest old patients? J Endocrinol Invest. 2022;45(9):1689-92.
272. Sciacchitano S, Capalbo C, Napoli C, Negro A, De Biase L, Marcolongo A, et al. Nonthyroidal illness syndrome (NTIS) in severe COVID-19 patients: role of T3 on the Na/K pump gene expression and on hydroelectrolytic equilibrium. J Transl Med. 2021;19(1):491.
273. Sciacchitano S, De Vitis C, D'Ascanio M, Giovagnoli S, De Dominicis C, Laghi A, et al. Gene signature and immune cell profiling by high-dimensional, single-cell analysis in COVID-19

patients, presenting Low T3 syndrome and coexistent hematological malignancies. J Transl Med. 2021;19(1):139.
274. Gong J, Wang D-k, Dong H, Xia Q-s, Huang Z-y, Zhao Y, et al. Prognostic significance of low TSH concentration in patients with COVID-19 presenting with non-thyroidal illness syndrome. BMC Endocrine Disorders. 2021;21(1):111.
275. Sun W, Xu C, Zhang Y, Zhu X, Yu F, Shi L, et al. Association between serum TSH levels and all-cause mortality in critically ill patients. Heliyon. 2024;10(4):e26168.
276. Pappa E, Gourna P, Galatas G, Manti M, Romiou A, Panagiotou L, et al. The prognostic utility of serum thyrotropin in hospitalized Covid-19 patients: statistical and machine learning approaches. Endocrine. 2023;80(1):86-92.
277. Kantrowitz LB, Peterson ME, Melián C, Nichols R. Serum total thyroxine, total triiodothyronine, free thyroxine, and thyrotropin concentrations in dogs with nonthyroidal disease. J Am Vet Med Assoc. 2001;219(6):765-9.
278. Nishii N, Okada R, Matsuba M, Takashima S, Kobatake Y, Kitagawa H. Risk factors for low plasma thyroxine and high plasma thyroid-stimulating hormone concentrations in dogs with non-thyroidal diseases. J Vet Med Sci. 2019;81(8):1097-103.
279. Ramsey IK, Evans H, Herrtage ME. Thyroid-stimulating hormone and total thyroxine concentrations in euthyroid, sick euthyroid and hypothyroid dogs. J Small Anim Pract. 1997;38(12):540-5.
280. Saridomichelakis MN, Xenoulis PG, Chatzis MK, Kasabalis D, Steiner JM, Suchodolski JS, et al. Thyroid function in 36 dogs with leishmaniosis due to Leishmania infantum before and during treatment with allopurinol with or without meglumine antimonate. Vet Parasitol. 2013;197(1-2):22-8.
281. Caldin M, Rocchi P, Zoia A, Botto A, Bertolini G, Zappa G, et al. Thyroid axis and adrenal activity in 28 day survivor and nonsurvivor dogs involved in recent road traffic accidents: A cohort study of 420 dogs. Research in Veterinary Science. 2020;132:243-9.
282. Elliott DA, King LG, Zerbe CA. Thyroid hormone concentrations in critically III canine intensive care patients. Journal of Veterinary Emergency and Critical Care. 1995;5(1):17-23.
283. Corsini A, Del Baldo F, Lunetta F, Ribichini S, Giunti M, Fidanzio F, et al. Total thyroxine, triiodothyronine, and thyrotropin concentrations during acute nonthyroidal illness and recovery in dogs. J Vet Intern Med. 2024;38(3):1345-52.
284. Gori E, Pierini A, Bartolomeo E, Ceccherini G, Pasquini A, Marchetti V. Serum Total Thyroxine Evaluation in Critically Ill Feline Patients. Veterinary Sciences. 2021;8(2):21.
285. Wakeling J, Moore K, Elliott J, Syme H. Diagnosis of hyperthyroidism in cats with mild chronic kidney disease. J Small Anim Pract. 2008;49(6):287-94.
286. ME P. Diagnosis and management of iatrogenic hypothyroidism. Consultations in Feline Internal Medicine, Volume 6-E-Book. 6. St. Louis, MO: Elsevier Health Sciences; 2016. p. 260-9.
287. Vaske HH, Schermerhorn T, Grauer GF. Effects of feline hyperthyroidism on kidney function: a review. Journal of Feline Medicine and Surgery. 2016;18(2):55-9.
288. Inc. ZCaZ. Truforma Operator's Manual: Thyroid-Stimulating Hormone (TSH) Test. 2022.
289. Silverstein D, Hopper K. Small Animal Critical Care Medicine-E-Book: Small Animal Critical Care Medicine-E-Book: Elsevier Health Sciences; 2014.