CITYU VETERINARY DIAGNOSTIC LABORATORY

Y1710, Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
Kowloon, Hong Kong
P: 3442-4849 | F: 3442-0819 | E: infovdl@cityu.edu.hk

Thyroid function tests and feline thyroid disease

Hyperthyroidism is the most common endocrine disease of geriatric cats. It is characterized by thyroid adenomatous hyperplasia, or benign thyroid adenoma, and the autonomous secretion of thyroid hormones. It most often affects both thyroid lobes, but may be unilateral. Thyroid carcinomas are rare in cats. Less often thyroid tissue is ectopic in the anterior mediastinum.

The majority of hyperthyroid cats are older than 8 years old (mean age 13 years). There is no sex or breed predisposition, although purebred cats have decreased risk of developing hyperthyroidism. Clinical signs may be mild to severe. **The most common clinical signs** include weight loss with polyphagia, increased activity and/or restlessness, PU/PD, and vomiting. Physical exam findings include a palpable thyroid nodule, tachycardia, tachypnea, heart murmur, cardiac arrhythmias, and dehydration.

There are several non-thyroidal diseases that can mimic the signs of hyperthyroidism. Therefore, the minimum database should include complete blood count (CBC), serum chemistry panel, and urinalysis (Ua) to evaluate for other diseases. If negative to other diseases, thyroid testing should be pursued to confirm the diagnosis of hyperthyroidism.

The main differential diagnoses for feline hyperthyroidism are diabetes mellitus, gastrointestinal disease (e.g. inflammatory bowel disease, gastrointestinal lymphoma), renal failure, and congestive heart failure.

In cats with hyperthyroidism, a **CBC** may reveal erythrocytosis and/or stress leukogram. The **chemistry panel** alterations may include mild to moderately increased liver enzymes (ALT, AST, and ALP), azotemia, hyperphosphatemia, and hypokalemia. Approximately 50% of cats have increased urine protein to creatinine ratios.

There are several tests that evaluate thyroid function and that can aid in the diagnosis of hyperthyroidism in cats that present with the typical clinical signs of this disease. These tests include serum **Total Thyroxine (T4), free T4 (fT4), Thyroid Stimulating Hormone (TSH), thyroid scintigraphy, Total Triiodothyronine (T3),** and dynamic thyroid testing via the **T3 suppression test**.

Before going over each of the thyroid gland function tests in more detail, it is important to have an understanding of the physiology of the thyroid gland.

Thyroid physiology

The functional unit of the thyroid gland is the follicle. The thyroid follicle consists of a single layer of cuboidal to columnar epithelial cells forming an acinus that surrounds a central core of colloid. Colloid is a proteinaceous material of mostly **Thyroglobulin (Tg)**. Tg is a glycoprotein that functions as reservoir for thyroid hormone.

Synthesis of thyroid hormones T4 and T3 requires iodide from the diet (Figure 1). Iodide enters from the extracellular fluid into the follicular cells and is secreted into the follicular lumen where is incorporated into the tyrosine residues of Tg. Iodinated tyrosine residues then conjugate to form T4 and T3 that remain bound to Tg until secreted.

CITYU VETERINARY DIAGNOSTIC LABORATORY

Y1710, Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
Kowloon, Hong Kong
P: 3442-4849 | F: 3442-0819 | E: infovdl@cityu.edu.hk

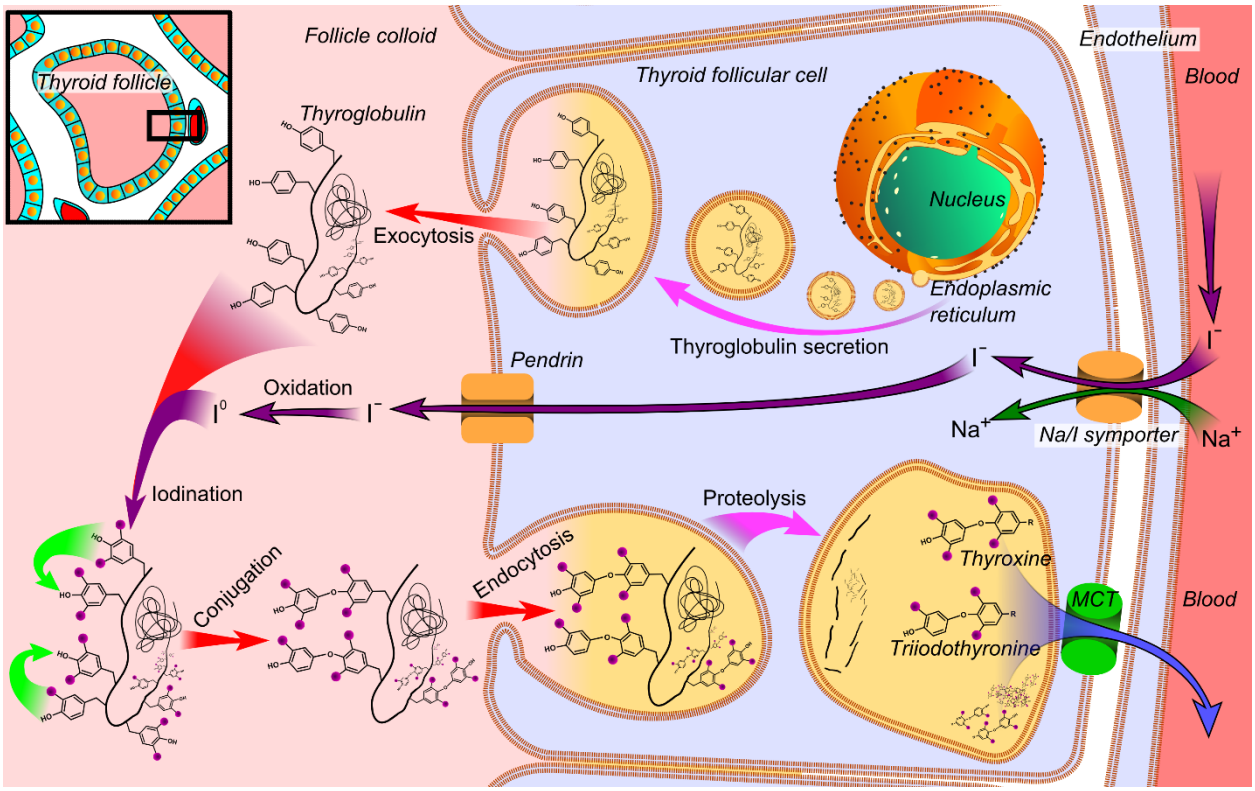

Figure 1. Synthesis of thyroid hormones within follicular cells. From Medical gallery of Mikael Häggström 2014; WikiJournal of Medicine 1.

Tg is stored in the follicular lumen, and during thyroid hormone secretion is ingested by the follicular cell via endocytosis from the colloid. The iodinated tyrosine residues separate from the large Tg molecule and T4, and to a much lesser degree T3, are released into the bloodstream.

This whole process is regulated by TSH and intrathyroidal factors (e.g., iodide intake). TSH secretion by the pituitary gland is modulated by thyroid hormones through a negative feedback regulatory mechanism (Figure 2). TSH secretion is suppressed by T3 derived from deionization of fT4 within the pituitary gland cells. **Thyrotropin-Releasing Hormone (TRH)** produced by the hypothalamus also regulates TSH production via not completely understood mechanisms. Other hormones that inhibit TSH secretion include dopamine, somatostatin, serotonin, and glucocorticoids. Prostaglandins and alpha-adrenergic agonists increase TSH secretion.

香港城市大學
City University of Hong Kong
VETERINARY DIAGNOSTIC LABORATORY

Y1710, Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
Kowloon, Hong Kong
P: 3442-4849 | F: 3442-0819 | E: infovdl@cityu.edu.hk

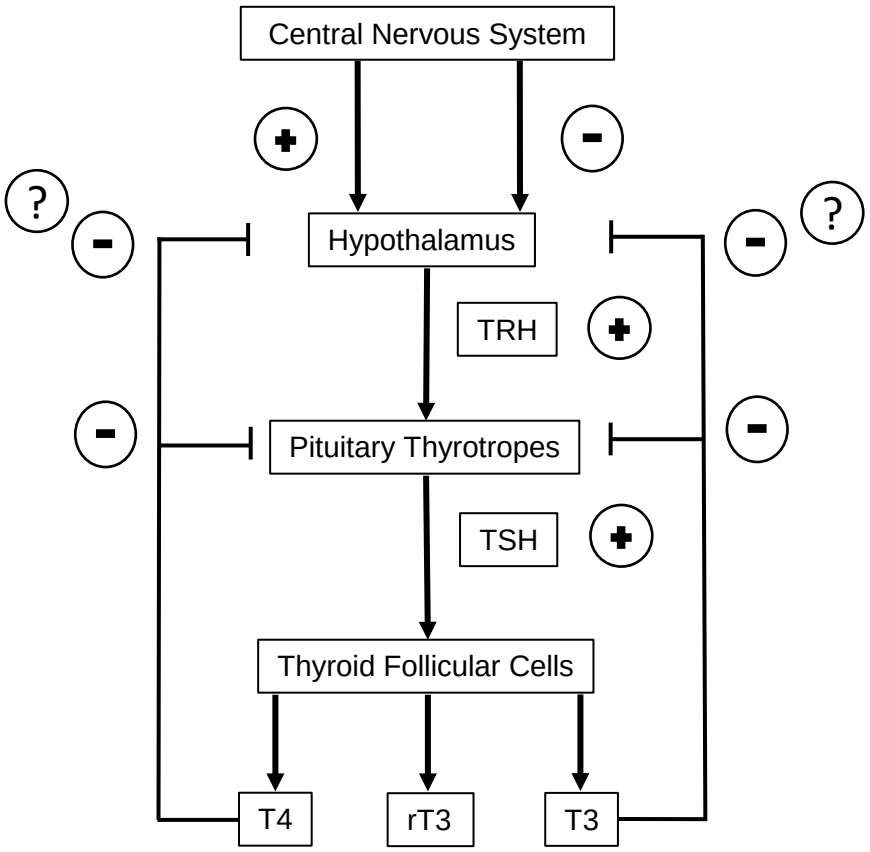

Figure 2. Regulation of thyroid hormone secretion. Modified from Scott-Moncrieff JC: Hypothyroidism. In Feldman EC, et al. editors: Canine & Feline Endocrinology, ed 4. St Louis, 2015, Elsevier

T4 is the most abundant of the thyroid hormones secreted by the thyroid gland. Only small amounts of T3 and **reverse T3 (rT3)** are produced. Once in circulation, >99% of T4 is bound to plasma proteins (thyroxine-binding globulin, albumin, thyroxine-binding prealbumin in the dog). The remaining Thyroxine is fT4 (<1%), which is biologically active, can enter cells, and suppresses TSH secretion by the pituitary gland. Protein-bound T4 functions as a reservoir of fT4.

Inside cells, fT4 is de-ionized into T3 or rT3 depending on the metabolic state of the cells at that point. T3 interacts with intracellular receptors leading to the physiologic actions of thyroid hormones, or binds to cytoplasmic binding proteins for storage. rT3 is biologically inactive, and is produced in periods of illness, starvation, or states of negative energy balance.

Thyroid function tests and hyperthyroidism in cats

Total Thyroxine (T4)

Older cats with suspected hyperthyroidism (e.g., weight loss despite eating well, thyroid nodule) are usually screened by determining serum T4. This test is inexpensive and specific. Hyperthyroidism can be confirmed if T4 is clearly high. Most cats with hyperthyroidism have T4 >60 nmol/L. However, up to 10% of all hyperthyroid cats and approximately 30% of cats with early or mild hyperthyroidism have T4 within normal limits. Additionally, concurrent non-thyroidal illness can suppress T4 to within normal limits. In these situations T4 is usually within the upper half of the reference interval or equivocal, and is unlikely to be below or within the low-end of the interval. When clinical signs are mild and early hyperthyroidism is considered likely, repeat T4 at a later date (in 4-8 weeks) to allow disease progression before retesting. If concurrent non-thyroidal illness that can be treated

香港城市大學
City University of Hong Kong
VETERINARY DIAGNOSTIC LABORATORY

Y1710, Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
Kowloon, Hong Kong
P: 3442-4849 | F: 3442-0819 | E: infovdl@cityu.edu.hk

is present, thyroid function testing should be delayed until non-thyroidal disease is resolved. If the clinical signs are severe however, additional testing such as fT4, and/or TSH would be recommended.

The following guidelines can be used for interpretation of T4:

Cat Normal	= 9.5-48 nmol/L
Consistent with hyperthyroidism	>48 nmol/L
Equivocal	= 25-48 nmol/L
Euthyroidism	in reference range

free T4 (fT4)

In reality, fT4 is the hormone that better reflects thyroid function. Compared to T4, fT4 is less affected by alterations in metabolism, protein binding, transport into cells, and intracellular binding, and non-thyroidal illness. fT4 is a sensitive test for hyperthyroidism; 95% of cats with occult hyperthyroidism have high fT4. However, fT4 may be less specific than T4 for hyperthyroidism in cats. Approximately 6-20% of euthyroid cats with non-thyroidal illness, and some clinically normal cats may have above normal fT4. **Most cats with a low T4 and a high fT4 are not hyperthyroid.** Therefore, fT4 should not be used as the single test for the diagnosis of feline hyperthyroidism. Rather fT4 may be a useful additional test in cats that are clinically hyperthyroid but have an equivocal serum T4.

The following guidelines can be used for interpretation:

Normal T4 with low or normal fT4 = Hyperthyroidism unlikely
Equivocal T4 with low or normal fT4 = Hyperthyroidism unlikely
Equivocal T4 with high fT4 = Hyperthyroidism likely
High T4 with high fT4 = Consistent with hyperthyroidism

If the serum total T4 and fT4 concentrations are not confirmatory, (and hyperthyroidism is suspected), determining TSH, the T3 suppression test or thyroid radionuclide imaging (scintigraphy) should be considered.

Thyroid Stimulating Hormone (TSH)

The T3 suppression test and thyroid scintigraphy are laborious tests and not readily available, while TSH is a rapid test that can aid in the diagnosis of hyperthyroidism in cats with clinical signs, when T4 and/or fT4 are within normal limits or equivocal (occult hyperthyroidism), or in cats with high fT4, but T4 within normal limits.

The current CLIA assay for TSH cannot accurately differentiate between low-normal and subnormal TSH in cats. However, almost all of hyperthyroid cats (98%) will have undetectable (<0.03 ng/mL) serum TSH concentrations, whereas most normal and sick euthyroid cats (69.9%) have detectable TSH (median TSH 0.05 ng/mL and 0.06 ng/mL, respectively). Although 30% of older euthyroid cats may have undetectable TSH, TSH can be considered as a highly sensitive, but a poorly specific test for feline hyperthyroidism. Therefore, TSH serum concentrations should be interpreted together with clinical signs, and serum T4 and fT4 concentrations. Combining TSH with T4 or fT4 increases the specificity of the test.

Consider the following guidelines for interpretation:

Detectable TSH = Hyperthyroidism unlikely
Undetectable TSH with high-normal, or equivocal T4 or fT4 = Consistent with early hyperthyroidism.
Undetectable TSH with either or both high T4 and fT4 = Consistent with hyperthyroidism.

High TSH serum concentrations are occasionally seen in cats after treatment with radioiodine and clinical signs consistent with hypothyroidism.

CITYU VETERINARY DIAGNOSTIC LABORATORY

Y1710, Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
Kowloon, Hong Kong
P: 3442-4849 | F: 3442-0819 | E: infovdl@cityu.edu.hk

Total Triiodothyronine (T3) and T3 suppression test

Determination of T3 should not be used as the sole test for the diagnosis of hyperthyroidism in cats. There are studies that suggest that 25-33% of hyperthyroid cats have T3 within normal limits.

The T3 suppression test is based on suppression of T4 production by the normal thyroid in response to the exogenous administration of synthetic T3. The protocol consists of baseline determination of T4 and T3, followed by oral administration of synthetic T3 every 8 h for 2 days and a final dose on day 3 (7 doses total). T4 and T3 are measured again 2 to 6 hours after the last dose. In euthyroid cats the second T4 should be suppressed (second T4 >50% lower than the baseline T4 typically excludes hyperthyroidism), whereas cats with hyperthyroidism fail to suppress or show minimal suppression. T3 is measured to confirm that synthetic T3 was appropriately administered; the second T3 should be higher than the baseline T3 regardless of thyroid status. If it is not, then lack of suppression may be due to failure to administer synthetic T3, and the test results should not be trusted.

Treatment and monitoring of feline hyperthyroidism

Treatment options include oral or transdermal antithyroid therapy (thioureylenes), radioactive iodine therapy, surgical thyroidectomy, and dietary iodine restriction. Prior to definitive treatment via radioactive iodine therapy or thyroidectomy, a clinical trial with methimazole is recommended to assess renal function.

Antithyroid therapy can be used to stabilize the patient prior to radioactive or surgical treatment, or long term as a sole treatment. The thioureylenes used are **methimazole** and **carbimazole.** These antithyroid drugs inhibit the synthesis of thyroid hormones by inhibiting the incorporation of iodine to tyrosine residues. The recommended starting dosage for methimazole is twice daily. Most hyperthyroid cats become euthyroid within 2-3 weeks of treatment when T4 should be monitored (Figure 3). Concurrent with every monitoring of T4, a CBC and chemistry panel should be done. The treatment aim is to reduce T4 to 10-30 nmol/L. If the cat is still hyperthyroid, the dosage is adjusted until the cat becomes euthyroid. If the T4 decreases below the reference interval, then dosage should be reduced and T4 rechecked in 1 week. Monitoring should be done every 2-3 weeks for the first 3 months of therapy. If hyperthyroidism is well controlled and there are no adverse effects, monitoring can be extended to every 3-6 months. Dosage and monitoring of transdermal methimazole and carbimazole are similar.

Treatment with methimazole does not involve the risk of developing permanent hypothyroidism. However, it may cause mild CBC changes such as leukopenia, lymphocytosis, and eosinophilia. Low numbers of cats may develop severe neutropenia and thrombocytopenia, and toxic hepatopathy. Because long-term methimazole treatment is not curative and abnormal thyroid tissue progressively grows, some cats may become completely resistant to the treatment, or will not tolerate the dose necessary to control the hyperthyroidism.

CITYU VETERINARY DIAGNOSTIC LABORATORY

Y1710, Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
Kowloon, Hong Kong
P: 3442-4849 | F: 3442-0819 | E: infovdl@cityu.edu.hk

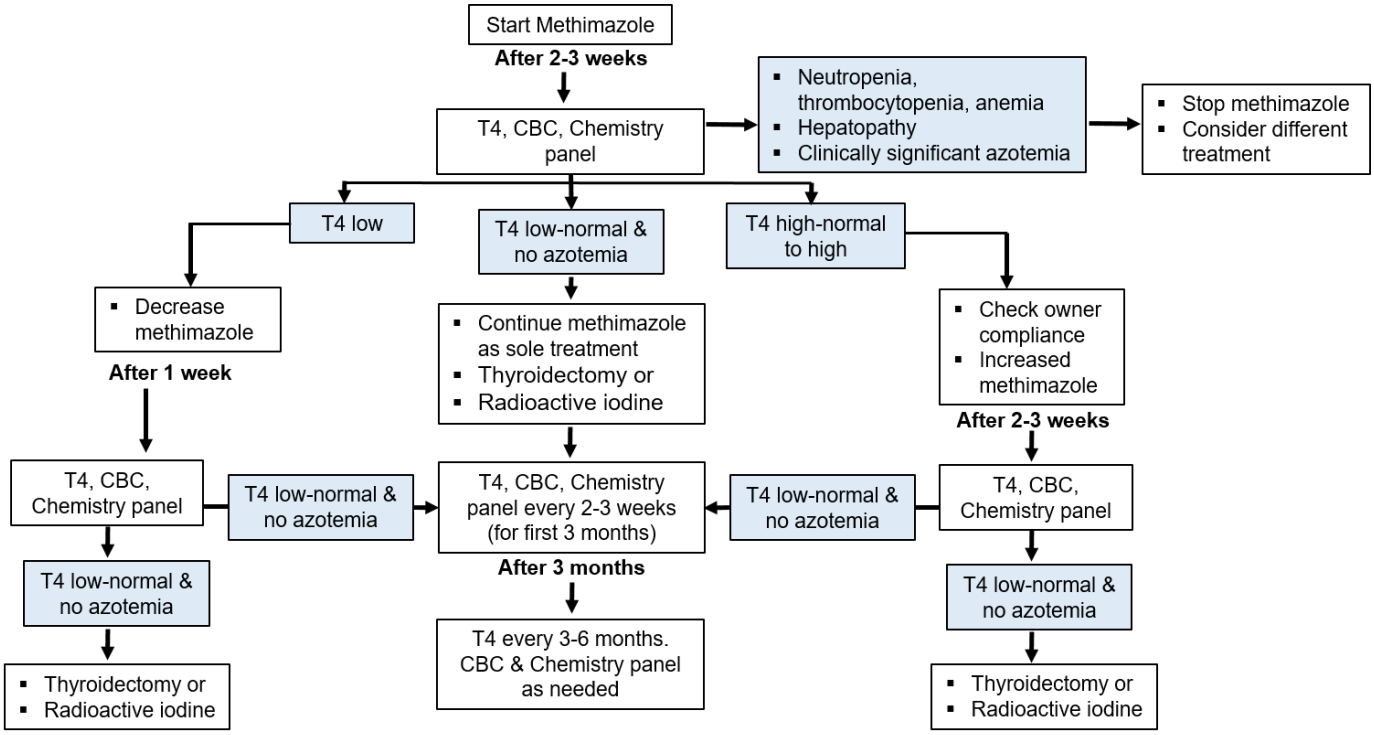

Figure 3. Monitoring Methimazole treatment in cats with hyperthyroidism. Modified from Scott-Moncrieff JC: Feline Hyperthyroidism. In Feldman EC, et al. editors: Canine & Feline Endocrinology, ed 4. St Louis, 2015, Elsevier

Curative treatment includes radioactive iodine therapy or surgical thyroidectomy.

Radioactive iodine therapy is the treatment of choice in most cases, as it is curative and there is low risk of iatrogenic hypothyroidism. Radioactive iodine is taken up by, and destroys the abnormal thyroid tissue, including ectopic thyroid tissue or metastatic thyroid carcinoma. Unless large doses are administered, the normal thyroid gland is usually spared because it is atrophied and does no uptake iodine. Once hyperthyroidism resolves and the normal feedback loops are reestablished, the atrophied thyroid tissue recuperates and normal thyroid function returns. Clinical improvement typically occurs within 2 weeks.T4 normalizes by 4-12 weeks after treatment. The disadvantages include lack of accessibility, expense, and the need for long isolation after treatment. Additionally, radioactive therapy should not be used in cats with underlying serious diseases that require therapy during the period of isolation, cats that develop azotemia after treatment with antithyroid drugs, or cats that do not tolerate hospitalization.

Surgical thyroidectomy is less commonly performed due to the increasing availability of radioactive iodine therapy. Thyroidectomy may be unilateral or bilateral. Normalization of thyroid function is usually achieved within 24-48 h of surgery. Unilateral thyroidectomy may result in transient hypothyroidism that tends to resolve within a few months. Bilateral thyroidectomy may result in clinical hypothyroidism that may require hormonal supplementation. Persistence or relapse of the hyperthyroidism is associated with incompletely removed abnormal thyroid tissue. Some cats may develop hypoparathyroidism with hypocalcemia due to concurrent removal of parathyroid glands. Indications for this treatment approach include cats with suspected thyroid carcinoma and cats with unilateral disease confirmed by thyroid imaging.

Dietary iodine restriction is based on the fact that the only function of ingested iodine is for thyroid hormone synthesis. Dietary iodine restriction reduces circulating thyroid hormone concentration into the normal range in hyperthyroid cats. However, normalization of T4 may take up to 180 days.

Of note is that treatment of hyperthyroidism and lowering of thyroid hormones may reveal occult chronic kidney disease as glomerular filtration rate decreases.

CITYU VETERINARY DIAGNOSTIC LABORATORY

Y1710, Yeung Kin Man Academic Building
City University of Hong Kong
83 Tat Chee Avenue
Kowloon, Hong Kong
P: 3442-4849 | F: 3442-0819 | E: infovdl@cityu.edu.hk

TSH and feline hypothyroidism

TSH can be used for the diagnosis of **iatrogenic hypothyroidism** in cats treated with radioactive iodine therapy, bilateral thyroidectomy, or anti-thyroid therapy. Thyroid hormones may decrease to subnormal concentrations within hours (surgery), days (anti-thyroid drugs), or weeks to months (radioactive iodine). It has been reported that 20-30% of cats treated with radioactive iodine develop hypothyroidism. In most cases, hypothyroidism is transient and resolves within weeks of treatment. However, some cats may become permanently hypothyroid.

Low T4 and/or fT4 in combination with increased TSH (RI: 0.03-0.3 ng/L) in a cat with clinical signs is consistent with hypothyroidism. The majority of cats (99%) with iatrogenic hypothyroidism have increased TSH. Clinical signs are usually mild, and include anorexia, lethargy, weight gain, poor hair coat, and alopecia. Although clinical disease may be mild, cats with iatrogenic hypothyroidism are more likely to become azotemic than euthyroid cats. Azotemic and hypothyroid cats show shorter survival than azotemic cats that are euthyroid. In cats with underlying chronic kidney disease, iatrogenic hypothyroidism can cause progression of renal disease and increase patient morbidity and mortality. Therefore, iatrogenic hypothyroidism should be avoided. Cats with hypothyroidism that persists 3-6 months after surgery or radioactive iodine treatment, develop clinical signs, and/or have progressive azotemia, should be supplemented with oral thyroid hormone.

Naturally-occurring hypothyroidism is rare in cats, especially in adults. Most cases are of congenital hypothyroidism in kittens. Of all thyroid tests, TSH is the most sensitive and specific for the diagnosis of feline hypothyroidism. Unlike in dogs, cats with hypothyroidism invariably show increased TSH due to loss of the normal negative feedback effect of thyroid hormones over the pituitary gland. Whereas T4 is a less sensitive test for the diagnosis of hypothyroidism in cats. TSH is less affected than T4 and fT4 by non-thyroidal illness; T4 and fT4 tend to decrease whereas TSH remains within reference limits. Unlike fT4, falsely high values for TSH are very rare in cats with non-thyroidal illness. Even if increased, TSH values are usually just slightly above the reference interval and not at the very high values typically seen in hypothyroid cats.

To confirm congenital hypothyroidism, T4 (+/- fT4) and TSH should be determined. **A low to low-normal T4 plus high TSH in a kitten with clinical signs are confirmatory of congenital hypothyroidism.** Clinical signs include decreased growth evident by 6-8 week of age, disproportionate dwarfism, lethargy, and retention of kitten hair coat and deciduous teeth. Although rare, iodine deficiency has been reported as a cause of hypothyroidism in kittens fed a strict all-meat diet.

TSH and radioactive iodine treatment

The atrophy of “normal” thyroid tissue in cats with hyperthyroidism, results from the negative feedback effects of high thyroid hormones produced by hyperplastic or neoplastic thyroid cells on pituitary THS secretion. Without TSH stimulus, iodine uptake by “normal” thyroid tissue falls and atrophy develops. Whereas function of the abnormal thyroid tissue is independent of TSH stimulus.

TSH determination can help evaluate for residual “normal” thyroid tissue prior to institution of radioactive iodine therapy. **Ideally, prior to radioactive iodine therapy, TSH should be undetectable**, as expected in hyperthyroid cats due to the negative feedback effect of high thyroid hormones on TSH secretion. If TSH is detectable, radioactive therapy should be postponed because there is an increased risk of cats becoming hypothyroid. The reasoning is that detectable TSH in a hyperthyroid cat indicates that pituitary TSH secretion is not fully suppressed and “normal” thyroid tissue may not be fully atrophied (mild or early hyperthyroidism). This residual “normal” tissue then may uptake radioactive iodine and be destroyed along with the abnormal hyperplastic or neoplastic target thyroid tissue. This increases the chances for iatrogenic hypothyroidism. It is recommended that treatment with radioactive iodine is postponed until TSH becomes undetectable.

References

Available upon request ☺ daniela.hernandez@cityu.edu.hk