Compendium

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Diagnostic Testing for Feline Thyroid Disease: Hypothyroidism

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Abstract: Although naturally occurring hypothyroidism is very rare in cats, iatrogenic hypothyroidism is a recognized complication of treatment for hyperthyroidism. However, confirming the diagnosis of hypothyroidism in cats is not generally straightforward. The potential for false-negative and false-positive results exists with all thyroid function tests, especially in older cats that may have concurrent nonthyroidal illness. Therefore, all thyroid function test results must be interpreted in light of the cat's history, clinical signs, and other laboratory findings. If a low to low-normal serum thyroxine (T_4) value is found in a cat that has been treated for hyperthyroidism, repeating the total T_4 analysis, determining free T_4 and thyroid stimulating hormone (TSH) concentrations, or performing a TSH stimulation test or thyroid scintigraphy may be needed to confirm the diagnosis.

For more information, please see the companion article, "Diagnostic Testing for Feline Thyroid Disease: Hyperthyroidism."

n cats, as in other species, hypothyroidism is the clinical syndrome that results from the chronic deficient secretion of the two thyroid hormones: thyroxine (T_4) and triiodothyronine (T_3).¹⁻⁴ Unlike dogs, in which primary hypothyroidism is common, naturally occurring hypothyroidism is extremely rare in adult cats, with only two documented cases reported.^{5,6} Most commonly, feline hypothyroidism is an iatrogenic complication associated with overtreatment of hyperthyroidism. Spontaneous hypothyroidism, when it does develop in cats, is seen most commonly as a congenital form in dwarf kittens.¹⁻⁴

Although many of the clinical features that develop in hypothyroid cats are similar to those seen in hypothyroid dogs, some major differences can make diagnosis more difficult in cats (**TABLE 1**).¹⁻⁴ First, hypothyroid cats may develop a poor appetite, a sign not reported in dogs with hypothyroidism. Second, hypothyroid cats rarely develop severe hair loss or total alopecia, relatively common signs in dogs. The major clinical signs of hypothyroidism in adult cats are not specific but can include lethargy, decreased appetite, and weight gain (**TABLE 1**).¹⁻⁴ Nonspecific cutaneous changes (e.g., nonpruritic seborrhea sicca, dull haircoat, excessive shedding or matting of hair) and obesity can develop, whereas hypothermia, and bradycardia are less common.¹⁻⁴

Iatrogenic hypothyroidism can develop during therapy with antithyroid drugs,⁷⁻⁹ after thyroidectomy,^{7,9,10} or following radioiodine therapy.^{7,11-14} Although early reports suggested that clinical signs associated with severe iatrogenic hypothyroidism in cats were uncommon and that most cats did not require treatment, it is now realized that milder degrees of iatrogenic hypothyroidism are relatively common and that these cats may benefit from thyroid replacement therapy. Many cats with mild or subclinical hypothyroidism fail to develop noticeable clinical features (**TABLE 1**).

A major potential benefit of treating iatrogenic hypothyroidism in cats is helping maintain renal function. It is well known that

	Congenital	latrogenic	Adult Onset
Lethargy	+++	+	++
Dermatologic signs	+	+	++
Weight gain or obesity	+	++	++
Poor appetite	+	+	++
Constipation	+++	+	+
Goiter	- 0ľ +++	- 0ľ +	_
Disproportionate dwarfism	+	-	-
Delayed closure of growth plates	+	-	-
Obvious clinical signs	+	-	+

Table 1. Clinical Features of Congenital, latrogenic, and Spontaneous Adult-Onset Hypothyroidism in Cats

+ = present, - = absent.

untreated feline hyperthyroidism leads to a reversible increase in glomerular filtration rate (GFR) and that successful treatment of hyperthyroidism results in a decrease in GFR, which can result in the development of azotemia if underlying chronic kidney disease (CKD) is present.^{2,15} To make matters worse, if iatrogenic hypothyroidism develops in cats with underlying CKD, GFR may fall even further, leading to a further decline in renal function.^{2,16} A recent report concluded that cats that developed iatrogenic hypothyroidism after treatment with antithyroid drugs or surgical thyroidectomy were at higher risk for development of azotemia and had reduced survival times.9 Therefore, even if no severe clinical signs associated with hypothyroidism are present in these cats, treatment of hypothyroidism might help increase GFR, as it has been reported to do in hypothyroid dogs,17 thereby improving kidney function and survival. As a result, it may be important to avoid, or at least minimize, iatrogenic hypothyroidism when treating hyperthyroid cats, many of which are likely to have some degree of preexisting CKD.9,15

This article reviews the common thyroid function tests currently recommended to diagnose hypothyroidism in cats. Because definitive diagnosis of this relatively common disorder is not always straightforward, this outline will concentrate on the diagnostic protocols used in the workup of cats suspected of having iatrogenic hypothyroidism.

Diagnosing Cats With Hypothyroidism

Correctly diagnosing feline hypothyroidism can be challenging, regardless of its etiology. Again, this syndrome rarely develops spontaneously.¹⁻⁴ Because hypothyroidism in adult cats is almost always iatrogenic, diagnosing this disorder starts with a history of the cat being treated for hyperthyroidism. Thereafter, the presumptive diagnosis of hypothyroidism is based on a combination of clinical features (e.g., lethargy, weight gain despite normal or decreased appetite (**TABLE 1**), physical examination findings (e.g., poor haircoat, obesity), routine laboratory test findings (e.g., mild, nonregenerative anemia, azotemia), and low circulating thyroid hormone concentrations.¹⁻⁴

The diagnosis of hypothyroidism currently relies largely on assessment of basal thyroid hormone analyses (i.e., serum T_4 , T_3 , and free T_4), as well as serum thyroid stimulating hormone (TSH) determinations. The greatest difficulty in interpreting these tests is the number of factors other than intrinsic thyroid function that can affect concentrations of thyroid hormones, including assay technique, nonthyroidal illness, and certain drugs (e.g., sulfon-amides).^{1,18-20} In clinical practice, four major factors can make the diagnosis of iatrogenic hypothyroidism difficult to confirm in cats.

- Concurrent diseases, common in older cats, can result in "euthyroid sick syndrome," characterized by falsely low serum thyroid hormone concentrations.^{18–20} As in dogs,²⁰ serum TSH concentrations may also be high in some of these cats,⁷ which may lead to an incorrect diagnosis of hypothyroidism.
- **2.** Cats are expected to gain weight and decrease activity level after successful treatment of hyperthyroidism. Therefore, the clinical signs associated with iatrogenic hypothyroidism

can overlap with those expected with a return to a euthyroid state.^{2-4,9}

- **3.** The classic routine laboratory abnormalities associated with hypothyroidism (anemia, hypercholesterolemia) are non-specific and inconsistent, especially in adult cats with mild or subclinical hypothyroidism.¹⁻⁴
- **4.** Many cats develop a marked transient decrease in total T_4 within the first month of therapy with iodine-131 or thyroidectomy. This transient hypothyroid state is followed by a return to euthyroidism over the next 3 to 6 months as the remaining normal thyroid tissue recovers and regains function.

Specific Thyroid Function Tests Used in Cats Serum T₄ Concentration

By definition, cats with hypothyroidism have deficient thyroid hormone secretion. Therefore, finding a low serum T_4 concentration is key in establishing a preliminary diagnosis of feline hypothyroidism. As in dogs, however, it is possible for a cat with mild or subclinical hypothyroidism to maintain a borderline serum T_4 concentration in the low end of the reference interval (e.g., 0.8 to 1.5 µg/dL; 10 to 20 nmol/L).

Again, while extremely important in establishing a diagnosis, a subnormal T₄ concentration alone is never definitive for hypothyroidism for two reasons. First, the serum T₄ concentration may be falsely or borderline low as a result of assay error. Practitioners should be aware of the assay techniques being used by their commercial or in-house laboratories. In general, serum T₄ can now be measured by four different assay techniques: radioimmunoassay (RIA), long considered to be the gold standard; chemiluminescent enzyme immunoassay (CEIA; Immulite Total T,, Siemens Medical Solutions Diagnostics); homogenous enzyme immunoassay (DRI Thyroxine [T₄] assay, Microgenics Corporation); and an ELISA test kit (SNAP Total T₄, IDEXX Laboratories) for in-house use. Although the correlation of serum T₄ concentrations between all of these assay methods is good, any of these techniques can provide serum T₄ values that are falsely low (or high). Compared with the gold standard, RIA, CEIA is most reliable. Serum T₄ results must always be interpreted in light of the cat's history, clinical signs, and other laboratory findings. If a low serum T₄ value is found in a cat that lacks clinical signs of hypothyroidism, especially if there is no history of treatment for hyperthyroidism or obvious nonthyroidal illness, the serum T₄ test should be repeated using a different technique, with RIA or CEIA being the preferred assay techniques in such cases. (For more information on these assays, see the companion article, "Feline Focus: Diagnostic Testing for Feline Thyroid Disease: Hyperthyroidism.")

Second, the serum T₄ concentration is often falsely low in cats with nonthyroidal illness, such as diabetes mellitus, hepatic disease, renal disease, and systemic neoplasia.^{18–20} In general, the severity of the illness correlates inversely with the serum T₄ concentration (i.e., sicker cats have lower serum T₄ concentrations).^{18,20} Because multiple diseases and other factors can falsely lower the serum T₄ concentration in cats, nonthyroidal disease must always be ruled out before considering a diagnosis of hypothyroidism (**FIGURE 1**).



Figure 1. Flowchart for diagnosis of iatrogenic hypothyroidism in cats. In general, it is best to wait at least 3 months after radioiodine therapy or thyroidectomy before embarking on a workup for permanent iatrogenic hypothyroidism, especially if the cat is not presenting with clinical features of hypothyroidism. However, if a subnormal T_4 value together with worsening azotemia develops within the first month or two of treatment, this workup for hypothyroidism is recommended.

Once assay error and nonthyroidal illness have been excluded, cats with suspected hypothyroidism and a low T_4 concentration still require additional testing to establish a definitive diagnosis. Further thyroid function tests such as measurement of serum free T_4 and canine TSH (cTSH) are recommended (**FIGURE 1** and **FIGURE 2**). If difficulties are encountered in confirming (or excluding) a diagnosis of hypothyroidism using these standard tests, thyroid scintigraphy or TSH stimulation testing may be indicated to confirm the disease.

Serum T, Concentration

In most cats with hypothyroidism, serum total T₃ concentrations are low to subnormal, correlating fairly well with the low T₄ values. By contrast, in dogs with hypothyroidism, serum T₃ generally remains within the reference interval.²¹ The feline thyroid gland lacks the deiodinase enzyme (i.e., type 1 iodothyronine deiodinase) needed to convert T₄ to T₃,²² Therefore, cats may not secrete very much T₃ directly from the thyroid gland, and circulating T₃ appears to be primarily derived from peripheral deiodination of T₄ in the liver and kidney. As thyroid function abates, it appears that some cats cannot compensate—as dogs and humans initially do—by increasing thyroid secretion of T₃, so circulating concentrations fall. Like total T₄, however, T₃ concentrations can also be suppressed in euthyroid cats with nonthyroidal illnesses.^{1,2,20}

Serum Free T₄ Concentration

Free T_4 is the non–protein-bound fraction of circulating T_4 that can enter cells, producing the biologic effect of thyroid hormone and regulating the pituitary feedback mechanism. Free T_4 accounts for less than 1% of circulating T_4 . Because only the free T_4 is biologically active, measuring free T_4 is considered a more sensitive test for diagnosing hypothyroidism. In addition, nonthyroidal illness influences free T_4 less than it influences the total $T_4^{-2,19,20}$ Therefore, free T_4 should be theoretically better at distinguishing a euthyroid cat with nonthyroidal disease from a hypothyroid cat.

Although measuring free T₄ concentration is generally a more accurate stand-alone test than total T₄ concentration, free T₄ is far from perfect for confirming feline hypothyroidism. First, the performance and accuracy of the current free T₄ assays are variable, and false-positive test results are common. Second, moderate to severe nonthyroidal illness can also falsely lower the free T₄ concentration, although to a lesser degree than seen with total T₄.^{2,19,20} In contrast, when free T₄ is measured by equilibrium dialysis, up to 20% of cats with nonthyroidal disease have a falsely high concentration.^{2,23} However, such a high free T₄ result, even if falsely elevated, would completely exclude a diagnosis of hypothyroidism.

As a thyroid function test, free T_4 is always best interpreted with corresponding total T_4 and TSH measurements (see "Serum

Compendium

Thyroid Hormone Panels," below). A low total T_4 value combined with a low free T_4 concentration (and high TSH value) is consistent with hypothyroidism, whereas low T_4 combined with normal or even high free T_4 is found in normal and hyperthyroid cats with nonthyroidal illness (**FIGURE 1** and **FIGURE 2**). As always, these thyroid test results must be combined with the cat's clinical presentation and history to help make the correct diagnosis.

Serum Thyroid Stimulating Hormone Concentration

In human patients, measurement of serum TSH concentration is commonly used as the first-line test of thyroid function.²⁴ The pituitary gland constantly monitors circulating levels of T_4 and T_3 , and if it senses the slightest decrease in these concentrations, it increases the secretion of TSH. Therefore, finding a high serum TSH value in a human patient is considered diagnostic for hypothyroidism, even if serum T_4 concentrations remain normal.²⁴

A specific assay for feline TSH is not yet available, but the commercially available cTSH assay cross-reacts with feline TSH

enough to enable its use as a diagnostic test for hypothyroid cats. In one of the reported adult cats with spontaneous hypothyroidism, the serum TSH concentration was high when measured with the cTSH assay.⁶ Similarly, many cats with suspected iatrogenic hypothyroidism develop high serum TSH concentration as measured by the cTSH assay.^{7,9} Based on these results, the cTSH assay has been touted as a good diagnostic test for feline hypothyroidism.^{9,25} However, the measurement of TSH concentrations is relatively new, and no one has published results of a large case series documenting the true predictive value of serum cTSH as a diagnostic test for feline hypothyroidism.

In a cat suspected of hypothyroidism, the finding of a high serum TSH value in combination with low serum concentrations of total or free T₄ can generally be considered diagnostic for hypothyroidism (**FIGURE 1** and **FIGURE 2**). This assay, however, is far from perfect. Similar to dogs, in which in which high TSH values are found in about 10% of cases with nonthyroidal illness,^{20,26} some cats with mild nonthyroidal illness—in particular, obese cats and cats with poorly controlled diabetes⁷—have high (false-positive) cTSH concentrations, even when they have mid- to high-normal T₄ and free T₄ concentrations. Similar findings have been reported in euthyroid, obese human patients.²⁷

In addition, it is common for high serum TSH to develop in cats treated for hyperthyroidism despite maintenance of completely normal concentrations of T_4 , free T_4 , or both (**FIGURE 2**, area B). Do these cats really have mild degrees of hypothyroidism? Should

they be treated with levothyroxine despite their normal circulating thyroid hormone values? Or are these serum TSH values falsely high, simply representing a TSH laboratory artifact? At this time, the answers to these questions remain unknown.

Finally, the high serum TSH concentrations in some cats with suspected iatrogenic hypothyroidism fail to decrease after adequate levothyroxine therapy. In some cats, serum TSH concentrations remain very high despite a rise in post-pill T_4 concentrations to the upper end of the reference interval. Physiologically, the rise in T_4 and T_3 should signal the pituitary gland to shut off TSH secretion,²⁴ so the failure of TSH to fall despite high circulating T_4 and T_3 calls into question the accuracy of the cTSH assay in these cats.

Obviously, a better TSH assay for feline hyperthyroidism is needed—particularly, a feline-specific TSH assay. However, until better TSH assays for cats are available, caution is advised in overinterpreting values in cats.

Serum Thyroid Hormone Panels

Differentiating hypothyroid from euthyroid cats can be challenging and may require evaluation of more than a single thyroid function test. Thyroid panels, which include serum total T_4 , free T_4 , total T_3 , and cTSH, are now commonly offered by many commercial laboratories. Evaluation of these thyroid panels can be very helpful in improving diagnostic sensitivity for hypothyroidism (**FIGURE 1** and **FIGURE 2**); however, these panels should be used for confirmation, rather than screening, as discordant results are very common.

Diagnostic Testing for Feline Thyroid Disease: Hypothyroidism



Figure 2. Scatterplot of T_4 (left panel) and free T_4 (right panel) versus TSH in 41 cats being monitored after treatment with radioiodine, methimazole, or surgical thyroidectomy. The vertical shaded area depicts the reference range limits for T_4 and free T_4 , whereas the horizontal shaded area depicts the reference range limits for TSH. On both scatterplots, the cats in area A have low concentrations of T_4 or free T_4 but high TSH values, consistent with hypothyroidism. The cats in area B have normal T_4 or free T_4 but high TSH concentrations, consistent with subclinical hypothyroidism or TSH laboratory artifact. The cat(s) in area C has/have a low T_4 or free T_4 concentrations but a normal TSH concentration, presumably due to nonthyroidal disease. The cats in area D have normal concentrations of T_4 , free T_4 , and TSH, consistent with euthyroidism.

For example, as noted above, it is not uncommon to see high cTSH concentrations with completely normal T_4 and free T_4 values in cats that have been treated for hyperthyroidism (**FIGURE 2**). Most of these cats do not have clinical signs of hypothyroidism, and the clinical significance of the high TSH concentration in this subgroup is unclear. In general, if levels of at least three of the four main hormones are abnormal and consistent with hypothyroidism (low to low-normal T_4 , free T_4 , and T_3 ; high TSH), the results can be considered diagnostic for hypothyroidism.

Thyroid Stimulating Hormone Stimulation Test

The TSH stimulation test provides important information for diagnosing hypothyroidism because it directly tests the thyroid's secretory reserve. A recombinant human TSH (rhTSH) preparation Thyrogen, Genzyme Corporation, Naarden, the Netherlands) has been validated for TSH stimulation testing in cats. ^{28,29} The testing protocol involves collecting samples for serum T₄ concentration before and 6 hours after IV administration of 25 to 200 µg of rhTSH.

In normal cats, administering exogenous rhTSH produces a consistent rise in serum T_4 concentration with at least a twofold rise in T_4 .^{28,29} Further studies are needed to validate the use of this test for diagnosing feline hypothyroidism, but hypothyroid cats tested to date showed little to no rise in serum T_4 after TSH stimulation.²⁹ The major disadvantage of this test is that rhTSH is extremely expensive, making it cost prohibitive for many owners.

Thyroid Scintigraphy

Thyroid scintigraphy is a nuclear medicine procedure that produces a visual display of functional thyroid tissue based on the selective uptake of various radionuclides by thyroid tissue.^{30,31} This test is considered the best imaging technique for cats (and dogs) suspected of having hypothyroidism because it can distinguish animals with hypothyroidism from those with a falsely low serum T₄ concentration.³²

In cats with hypothyroidism secondary to treatment with thyroidectomy or radioiodine, thyroid scintigraphy typically reveals decreased or even absent radionuclide uptake (i.e., the thyroid gland is not visible on the scan; **FIGURE 3**).^{6,31} Cats with a falsely low serum thyroid hormone concentration secondary to illness or drug therapy have a normal thyroid image. This procedure is of no benefit in diagnosis of methimazole-induced hypothyroidism, however.⁸

Unfortunately, few veterinarians have access to the equipment needed to obtain thyroid images or perform thyroid uptake determinations.

Diagnostic Protocol for Cats With Suspected latrogenic Hypothyroidism

After a cat has been treated for hyperthyroidism with radioiodine, surgical thyroidectomy, or methimazole, I recommend monitoring the cat with a complete physical examination, as well as routine laboratory testing (e.g., complete blood count, serum chemistry panel, complete urinalysis) and total T_4 determinations at 1 and



Figure 3. (A) Thyroid scintigraphy in a euthyroid cat. In normal cats, the thyroid gland appears on thyroid scans as two well-defined, focal (ovoid) areas of radionuclide accumulation in the cranial to middle cervical region. The two thyroid lobes are symmetrical in size and shape and are located side by side. Activity in the normal thyroid closely approximates activity in the salivary glands, with an expected "brightness" ratio of 1:1. (B) Thyroid scintigraphy in a cat with iatrogenic hypothyroidism. This cat was treated with high-dose iodine-131 for thyroid carcinoma 3 months previously. The serum concentrations of T_4 and free T_4 were subnormal, and the TSH value was high. Notice that no residual thyroid tissue is present, confirming the diagnosis.

3 months (**FIGURE 1**). If the serum T_4 level falls to a subnormal or low-normal value and iatrogenic hypothyroidism is suspected, a complete thyroid profile (serum T_4 , free T_4 , T_3 , and TSH concentrations) is recommended to help establish the diagnosis (**FIGURE 1** and **FIGURE 2**). The combination of low to low-normal serum concentrations of T_4 , free T_4 , and T_3 , together with a clearly high TSH value, can be considered diagnostic for hypothyroidism.

No matter what treatment is chosen for hyperthyroidism, the ideal post-treatment serum T_4 concentration is a value in the midnormal range. For example, if the T_4 reference interval is 0.8 to 4.0 µg/dL (10 to 50 nmol/L), my goal is to maintain the T_4 value between 1.5 and 3.0 µg/dL (20 and 40 nmol/L). Recent research indicates that both mild hyper- and hypothyroidism are deleterious to kidney function and may worsen existing CKD.^{9,33}

As in dogs and people with hypothyroidism, the finding of a high serum TSH concentration, together with low serum total and free T_4 values, is consistent with primary hypothyroidism (**FIGURE 1** and **FIGURE 2**). Cats with nonthyroidal illness (such as CKD) commonly have low serum total and free T_4 concentrations, but these cats generally maintain normal values for serum TSH, which helps exclude iatrogenic hypothyroidism.

For most cats, I recommend waiting at least 3 months after radioiodine therapy or thyroidectomy before embarking on a workup for permanent iatrogenic hypothyroidism, especially if the cat is not presenting with clinical features of hypothyroidism. Many cats treated with radioiodine or unilateral thyroidectomy go through a period of transient hypothyroidism after treatment. Most of these cats have some remaining normal thyroid tissue that has been chronically suppressed by hyperthyroidism. With time, this normal thyroid tissue may start to function normally again to restore euthyroidism. However, clinicians should diagnose or exclude hypothyroidism as soon as possible in cats with renal disease because hypothyroidism, treatment for hyperthyroidism, and chronic renal disease all lower the GFR. The combined effect of these three factors can lead to severe renal azotemia or even renal failure. In hypothyroid cats with concurrent CKD, instituting T_4 replacement therapy and increasing serum thyroid hormone concentrations back into the reference interval may help raise the GFR to an acceptable level and reduce azotemia.⁹

Conclusion

Knowledge about hypothyroidism in cats has increased markedly over the last few years. Diagnosing iatrogenic hypothyroidism can be challenging in some cats because of the concomitant presence of another disease (e.g., CKD) or a transient decrease in total T_4 within the first months of therapy for hyperthyroidism with surgery or radioiodine.

However, there is much yet to learn: do cats that develop a high serum TSH concentration but maintain normal serum concentrations of T_4 or free T_4 have subclinical hypothyroidism? In other words, is the high circulating TSH concentration seen in these cats a compensatory mechanism that allows a cat with lower-thannormal amounts of residual thyroid tissue to maintain euthyroidism? Or is the high TSH a false-positive result? Although the answers to those questions remain to be determined, some obese and diabetic cats show false-positive (high) cTSH concentrations, despite maintaining serum T₄ and free T₄ concentrations within the middle of the reference interval (i.e., not low or low-normal). In further support of possible false-positive results, the high serum TSH concentrations in some cats with suspected iatrogenic hypothyroidism fail to decrease after adequate levothyroxine therapy, as would be expected based on the known negative feedback effects of thyroid hormones on pituitary TSH secretion.

The bottom line is that all thyroid function test results must be interpreted in light of the cat's history, clinical signs, and other routine laboratory findings, especially renal function test results. Therapeutic or monitoring decisions should never be based on the thyroid laboratory value(s) alone—always remember to look at the cat!

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