Hypothyroidism and Myxedema Coma

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ABSTRACT: Hypothyroidism is a common endocrinopathy in dogs but is rare in cats. Lymphocytic thyroiditis and idiopathic thyroid atrophy are common causes of this condition. Specific thyroid function tests, in conjunction with clinical signs and physical examination findings, are used to help confirm a diagnosis of hypothyroidism. This disease can be managed with synthetic hormone supplementation and has an excellent prognosis. Myxedema coma is a rare and potentially fatal manifestation of severe hypothyroidism that can be successfully treated using intravenous levothyroxine.

Hypothyroidism is a frequently diagnosed endocrinopathy in dogs1,2 but a rare phenomenon in cats. The thyroid, under the influence of thyrotropin (thyroid-stimulating hormone [TSH]), produces the hormones thyroxine (T4) and 3,5,3’-triiodothyronine (T3). T4 and T3 have many effects on cellular metabolism, and their levels in the body are tightly regulated. Dysregulation of T3 and T4 levels has far-reaching effects. The signs of thyroid hormone deficiency are vague, nonspecific, and not pathognomonic. No single test can be conducted to make a definitive diagnosis. Instead, a diagnosis of hypothyroidism is made based on a combination of clinical signs, physical examination findings, biochemical abnormalities, and thyroid function tests. With this combination of tests, a diagnosis of hypothyroidism can be made with confidence. However, clinicians must keep in mind that nonthyroidal illness, some medications, physical activity level, and antithyroglobulin antibodies can alter the results of thyroid function tests. Once a diagnosis has been made, this disease can be easily controlled with thyroid hormone supplementation. A rare but serious complication of severe hypothyroidism is myxedema coma.

PHYSIOLOGY

Iodine and tyrosine are the basic substrates involved in thyroid hormone synthesis (Figure 1). Dietary iodide is actively transported into thyroid follicular cells and oxidized to iodine by thyroperoxidase. Iodine then binds to tyrosine residues on thyroglobulin to form moniodotyrosine (MIT) and diiodotyrosine (DIT). Coupling of MIT and DIT forms both T3 (MIT–DIT) and T4 (DIT–DIT), which are bound to thyroglobulin and stored in colloid. Under the control of TSH, thyroglobulin undergoes proteolysis in phagolysosomes, releasing T3 and T4.3,4 Thyroid hormones are water-insoluble, and their ability to circulate...
depends on binding to $T_4$-binding globulin, $T_4$-binding prealbumin, or albumin. Most thyroid hormone (i.e., $>99\%$) is protein bound, with the remaining unbound portion being the metabolically active or “free” form. These binding proteins are reservoirs for circulating thyroid hormone and allow the free hormone level to be maintained within a very narrow range. $T_4$ is the main secretory product of the thyroid. However, $T_3$ is more biologically active and is most effective in binding to and activating the thyroid hormone nuclear receptor. Once in peripheral tissues, $T_4$ is deiodinated to $T_3$ before receptor binding. Most $T_3$ (i.e., 40\% to 60\%) is derived from extrathyroidal deiodination of $T_4$. The production and release of thyroid hormones are controlled by a classic negative feedback mechanism (Figure 2). The hypothalamic–pituitary–thyroid axis is responsible for maintaining control of extrathyroidal hormone levels. The hypothalamus produces thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to produce TSH, which then stimulates the thyroid. TRH and TSH production is down-regulated by circulating thyroid hormones, particularly $T_3$. 

### PATHOPHYSIOLOGY

Hypothyroidism can be classified as acquired or congenital. Acquired hypothyroidism can be primary, sec-
Secondary, or tertiary and usually affects adult dogs, with the average age at diagnosis being 7 years. Primary hypothyroidism is associated with a defect localized to the thyroid. With this form of hypothyroidism, the thyroid tissue has been destroyed or replaced and thus becomes less responsive to TSH. Therefore, T3 and T4 levels gradually decline, with a compensatory increase in TSH (Figure 3).

There are two common histologic forms of primary hypothyroidism: The first, lymphocytic thyroiditis, is thought to be an immune-mediated process and eventually results in thyroid atrophy. The second, idiopathic thyroid atrophy, is a separate form of thyroid destruction that does not demonstrate an inflammatory component. Together, these processes account for 95% of the clinical cases of hypothyroidism in dogs. This is comparable with humans, in which 99% of hypothyroidism is the result of these mechanisms.

In dogs, lymphocytic thyroiditis and idiopathic thyroid atrophy each accounts for half of the reported cases. Lymphocytic thyroiditis is characterized by chronic and progressive lymphocytic infiltration and destruction of the thyroid. Cytotoxic T cells set up inflammation, leading to thyrocyte destruction and parenchymal fibrosis. This process is gradual and accounts for the slow onset of clinical signs associated with hypothyroidism. The immune-mediated process is associated with production of autoantibodies, predominantly against thyroglobulin. However, autoantibodies against T3 and T4 have been reported. Although T3 and T4 are haptens, they are attached to thyroglobulin, which appears to act as the antigenic stimulus for antibody production. This differs from the process in humans, in which the immune target is thyroperoxidase.

Recent vaccination may cause an elevation in antithyroglobulin antibodies unassociated with primary hypothyroidism. Autoantibodies crossreact with T4 assays. This is clinically important because when autoantibodies are present, the total serum T4 level can be elevated into the reference or hyperthyroid ranges, causing clinicians to miss a diagnosis of hypothyroidism.

Secondary and tertiary hypothyroidism are rare. In secondary hypothyroidism, the defect is localized to the pituitary, and the ability to synthesize and secrete TSH is impaired. Secondary hypothyroidism may be caused by pituitary tumors, congenital malformation of the pituitary, infection, or TSH suppression. TSH suppression can be caused by drugs, hormones, or concurrent illness. Tertiary hypothyroidism is hypothalamic in origin, and production of TRH is either decreased or nonexistent. Tertiary hypothyroidism has not been reported in the veterinary literature.
demonstrate increased thyroid hormone levels in response to TSH or TRH stimulation, respectively.

Congenital hypothyroidism, which is rare in veterinary medicine, is caused by inherited defects or by exposure of the fetus or newborn to either an excess or a deficiency of dietary iodine. Congenital hypothyroidism is categorized as goitrous or nongoitrous. Goiter, the term for enlargement of the thyroid, develops when there is increased release of TSH, along with an intact thyroid TSH receptor. Clinical signs of congenital hypothyroidism include developmental delays, both mental and physical, and dwarfism. An autosomal recessive form of congenital hypothyroidism has been reported in toy fox terriers, giant schnauzers, and Abyssinian cats. Affected animals have a thyroid peroxidase deficiency. Genetic testing is available to detect carrier fox terriers.

CLINICAL SIGNS AND ROUTINE BLOOD ANALYSIS

Clinical signs associated with hypothyroidism are vague and involve many different systems (see box on this page). The most commonly reported clinical signs include dermatologic abnormalities, weight gain, lethargy, and weakness. Most changes appear to be secondary to decreased metabolism due to a lack of circulating thyroid hormones.

Dermatologic changes, including alopecia, seborrhea, and pyoderma, are commonly associated with hypothyroidism. However, changes in the epidermis and haircoat are often breed specific and are not noted in every patient. The value of skin biopsies is controversial because many cutaneous changes are nonspecific and biopsy specimens from different endocrinopathies may demonstrate similar changes. However, certain findings, including dermal thickening, myxedema, and vacuolation of arrector pili muscles, are most characteristic of hypothyroidism.

Bilateral symmetric nonpruritic truncal alopecia is reported in 88% of hypothyroid dogs. Thyroid hormones are required for initiation of anagen (active hair growth). In hypothyroid animals, most hair follicles are retained in telogen (i.e., the quiescent or resting phase of the hair cycle). Without thyroid hormones, the haircoat becomes dry, dull, and brittle. Hair loss is noted in areas of increased wear and usually includes the ventral thorax and neck, ventral abdomen, and tail. Loss of primary hair is most common with retention of guard hairs, resulting in a short, fine haircoat.

Hyperpigmentation may be noted in areas of alopecia. Other skin changes include dry scaly skin, pyoderma, dermatitis, seborrhea, hyperkeratosis, myxedema, and otitis externa. Thyroid hormone enhances the lymphoid immune response. In the hypothyroid state, there is decreased T-cell function and humoral immunity. This decrease in local immunity causes the skin to become more susceptible to infection. Pyoderma has been reported in 14% of dogs with hypothyroidism. Generalized demodicosis and Malassezia spp infections are common. An increased incidence of otitis externa also tends to be noted compared with the incidence in non-hypothyroid dogs. Primary dermatologic conditions such as alopecia, dry skin, and seborrhea are nonpruritic, but pruritis often accompanies secondary parasitic, yeast, or bacterial infection.

Neurologic abnormalities are rare. Most neurologic signs are associated with polyneuropathy and include weakness, facial nerve paralysis, vestibular signs (usually peripheral), and hyporeflexia. Segmental demyelination and axonopathy are the likely pathogenesis of these clinical signs. Megaesophagus and laryngeal paralysis have both been suggested to be associated with hypothyroidism; however, no data support this association. A causal relationship between hypothyroidism and myasthenia gravis has not been proven. Central nervous system signs, including seizures, ataxia, behavior changes, and coma, are rare. They may result from myxedema, lack of thyroid hormone, hyponatremia, or decreased blood flow to the brain.

Several reproductive abnormalities have been suggested to be associated with hypothyroidism. In males, these include decreased fertility, testicular atrophy, poor semen motility, and decreased libido. In females, hypothyroidism has been suggested to be associated with pro-
longed interst SY periods, failure to cycle, decreased libido, and inappropriate mammary gland development. No data have supported an association between decreased thyroid hormone levels and reproductive failure in males or females. When reproductive failure is detected, causes besides hypothyroidism must also be investigated.

Cardiovascular abnormalities, although rare, have been reported. Cardiovascular signs may be secondary to problems with conduction or direct myocardial effects. Bradycardia, arrhythmias, decreased conduction, decreased contractility, and diastolic dysfunction have been reported. In the hypothyroid state, there is a decreased β-adrenergic receptor number, accounting for decreased contractility and lower heart rates. In contrast to humans, congestive heart failure has not been documented secondary to hypothyroidism in dogs. Ocular changes can include corneal cholesterol deposits, keratoconjunctivitis sicca, and conjunctivitis, although these signs are reported in less than 1% of all hypothyroid dogs.

Hypercholesterolemia, hypertriglyceridemia, and hyponatremia are commonly noted in serum biochemistry results (see box on this page). These changes are the result of the decrease in normal lipid metabolism accompanying hypothyroidism. Hypothyroid dogs have increased very-low-density lipoproteins, low-density lipoproteins, and high-density lipoproteins. Increased triglyceride levels may play a role in the development of pancreatitis, although this association has not been proven. Elevated levels of cholesterol and triglycerides have been associated with atherosclerosis in dogs, although this is rare.

Anemia is another common finding, affecting 28% to 32% of hypothyroid dogs. The anemia is usually normochromic, normocytic and nonregenerative and likely results from one of or a combination of three mechanisms: There may be decreased erythropoietin production, a reduced response of progenitor cells to erythropoietin, or decreased stimulation of early hematopoietic stem cells. The hypothyroid state does not affect the erythrocyte life span.

A commonly requested initial screen of thyroid function is the total T₄ level test, which measures both protein-bound and free T₄ levels. The total T₄ level is a direct assessment of the functional ability of the thyroid tissue to produce hormone. A decreased total T₄ level is a common finding in hypothyroid animals; however, this is not diagnostic of hypothyroidism and necessitates more specific testing to confirm the diagnosis. The total T₄ level can be measured by ELISA, chemiluminescence, or radioimmunoassay. There is indication that in-house ELISA is less reliable than radioimmunoassay.

Measurement of the endogenous TSH level is available using a canine assay. Because of crossreactivity, this assay may also be used in cats. In the hypothyroid state, the TSH level would be expected to be elevated due to loss of negative feedback. The TSH level test has high specificity and low sensitivity. Because total or free T₃ and TSH levels are both elements of the feedback

**Common Laboratory Findings Associated with Hypothyroidism**

<table>
<thead>
<tr>
<th>Serum biochemical abnormalities</th>
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<tbody>
<tr>
<td>• Hypercholesterolemia</td>
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<td>• Hyperlipidemia</td>
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<td>• Hypertriglyceridemia</td>
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<tr>
<td>• Hyponatremia</td>
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<table>
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<tr>
<th>Complete blood count abnormality</th>
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<tr>
<td>• Nonregenerative anemia (usually normochromic, normocytic)</td>
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</table>

**THYROID FUNCTION TESTING**

The diagnosis of hypothyroidism is complex. The TSH stimulation test is a reliable single test used to diagnose hypothyroidism and is considered the gold standard. However, there is limited access to test reagents, and the cost is often prohibitive. Other tests are available to help clinicians evaluate thyroid function, thyroid hormone levels, and antithyroglobulin antibody levels. These tests include total T₄, endogenous canine TSH, free T₃, antithyroglobulin antibodies, anti-T₃ antibodies, anti-T₄ antibodies, total T₃, free T₃, and reverse T₃.

Assessment of total thyroxine as a screening test in combination with thyroid-stimulating hormone assessment as a confirmatory test are appropriate for obtaining a diagnosis of hypothyroidism. Free thyroxine may be used when initial test results are unclear.
mechanism of the hypothalamic–pituitary–thyroid axis, they should be interpreted together. In other words, to accurately understand the significance of a TSH level, the clinician must know the total or free T₄ level. Current methods of assessing TSH levels are not sensitive at low levels. Therefore, TSH cannot be used in the diagnosis of secondary hypothyroidism.

The free T₄ level test measures the metabolically active portion of the total T₄ level. This fraction of the hormone can enter the cell, be converted into T₃, and interact with the thyroid hormone receptor. Hypothyroid animals would be expected to have a low free T₄ level. This test, like the total T₄ level test, is most valuable as a screening test. Concurrent illness has less effect on the free T₄ level compared with the total T₄ level. However, glucocorticoids, phenobarbital, and hyperadrenocorticism have been noted to decrease the free T₄ level. Different methods can be used to measure the serum free T₄ level. Measurement by equilibrium dialysis has been demonstrated to be the most reliable compared with radioimmunoassay. The equilibrium dialysis method also mitigates the influence of antithyroglobulin antibodies, leading to the best likelihood of an accurate test result.

Immune–mediated thyroiditis may result in the production of antithyroglobulin or anti-T₃ or -T₄ antibodies. It is possible to test for antithyroglobulin antibodies, and a positive titer is predictive of immune-mediated thyroiditis and suggestive of hypothyroidism. Anti-T₃ and -T₄ antibodies may create a problem in the diagnosis of hypothyroidism. The antibodies are similar to those of T₃ and T₄ and can crossreact to falsely elevate assay levels. Therefore, if anti-T₄ antibodies are present, the total T₄ level will reportedly be higher than it actually is. This is of most concern with animals in which the total T₄ level is truly just below the normal range. With the presence of anti-T₄ antibodies, these animals may actually appear to be euthyroid, thus delaying diagnosis and treatment of hypothyroidism. Free T₄, measured by dialysis, is not affected by the presence of antithyroglobulin or anti-T₃ or -T₄ antibodies. In some situations, the antithyroglobulin antibodies are positive, but the total and free T₄ levels are well within normal range, and the animal does not exhibit clinical signs associated with hypothyroidism. These cases demand close monitoring and reevaluation because they may be at risk of developing hypothyroidism.

For many years, the TSH stimulation test was used to diagnose hypothyroidism. This test was routinely conducted using pharmaceutical-grade bovine TSH. With the introduction of recombinant human TSH, production of pharmaceutical-grade bovine TSH was halted. Studies have demonstrated that recombinant human TSH can be used in both dogs and cats safely and effectively to conduct the TSH stimulation test. Adverse side effects of recombinant human TSH in humans include headache and nausea; no adverse effects have been reported in cats or dogs. Recombinant human TSH is very expensive, and although its use is validated, it is unlikely to become routine and displace the total and free T₄ tests and the TSH stimulation test as the preferred diagnostics.

Serum total T₃ measurement is an unreliable indicator of thyroid function. The total T₃ level has been demonstrated to be normal in up to 90% of all hypothyroid dogs. In case-controlled studies, the reverse T₃ level has not been validated in companion animals. Therefore, evaluation of total T₃, free T₃, and reverse T₃ levels is not routinely recommended to assess thyroid function in dogs.

Another tool has recently become available to assist in the diagnosis of hypothyroidism. Two studies have indicated that ultrasonography of the thyroid is helpful in distinguishing hypothyroid and euthyroid dogs. The studies demonstrated significant differences in thyroid volume and echogenicity between hypothyroid and euthyroid patients. There was no significant difference between euthyroid and sick euthyroid subjects. These studies concluded that ultrasonography can be an adjunctive diagnostic tool to assist in the diagnosis of canine hypothyroidism. Limitations of this test include the need for high-quality ultrasonography equipment and a skilled, trained operator. In the future, this test may become more widespread and routine.

All available tests can be used to help diagnose hypothyroidism (Table 1). Investigation of hypothyroidism should be based on an increased index of suspicion. A complete blood count, serum biochemistry profile, and urinalysis are helpful in ruling out the pres-
ence of nonthyroidal illness (Figure 4). The next step would be to run a highly sensitive test (i.e., total T₄ level) for screening and a more specific test (i.e., canine TSH level) to help confirm the diagnosis (Table 2). In some instances, a concurrent illness may not be able to be resolved (e.g., diabetes mellitus, chronic renal failure); because TSH is minimally affected by concurrent disease, it is still recommended to proceed with these tests. The data in Table 2 demonstrate that by using a combination of tests, clinicians can obtain a highly reliable result. However, in some situations, test results are unclear. This occurs with early (subclinical) hypothyroidism, secondary hypothyroidism (sick euthyroid), anti-T₄ antibodies, or other causes of thyroid hormone suppression. In these situations, obtaining a free T₄ level can be a secondary test to help indicate an animal’s thyroid status. In some instances, early (subclinical) hypothyroidism or unclear results may be detected; a rational approach would be to retest the animal in 4 weeks.

### OTHER FACTORS THAT ALTER THYROID FUNCTION TEST RESULTS

Besides sick euthyroid syndrome, additional factors can alter the results of thyroid function tests, potentially

<table>
<thead>
<tr>
<th>Table 1. Available Tests for the Diagnosis of Hypothyroidism</th>
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<tr>
<td><strong>Test/Tool</strong></td>
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<td>Total T₄</td>
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<td>Canine TSH</td>
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<td>Free T₄</td>
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<td>Antithyroglobulin antibodies</td>
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<tr>
<td>TSH stimulation test</td>
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<tr>
<td>Total or free T₃</td>
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<td>Reverse T₃</td>
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<td>Ultrasonography</td>
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</table>
Clinical suspicion of hypothyroidism based on clinical signs, physical examination findings, and history

Is there evidence of nonthyroidal illness?

Yes

Is it a resolvable nonthyroidal illness?

No

Conduct initial thyroid tests (total T₄ and TSH levels)

Low total T₄ and increased TSH levels

Hypothyroid; start treatment

Low total T₄ and low TSH levels

Conduct secondary thyroid test (free T₄)

Low free T₄ level

Decreased TSH level

Secondary hypothyroid (sick euthyroid)

Normal free T₄ level

Normal or increased TSH level

Early hypothyroid

Euthyroid

Normal total T₄ and normal TSH levels

If clinical signs persist, retest in 4 wk

Figure 4. Diagnosis of hypothyroidism.
resulting in misdiagnosis (see box on this page). Most reported factors cause an artificial decrease in thyroid hormone levels. Many drugs affect thyroid hormone levels and may result in an animal developing clinical signs of hypothyroidism. The exact mechanisms for each factor are not completely and individually understood. However, decreased binding of thyroid hormone to proteins and the ability of certain drugs to bind iodine, making it less available for thyroid hormone synthesis, are two mechanisms explaining how certain drugs can cause decreased thyroid hormone levels. Sulfonamides,\textsuperscript{18,58,59} glucocorticoids,\textsuperscript{60,61} phenobarbital,\textsuperscript{62,63} clomipramine,\textsuperscript{64} and NSAIDs\textsuperscript{18,65} have all reportedly decreased circulating thyroid hormone levels in animals. Sulfonamides inhibit thyroid peroxidase and decrease iodine organification and thus production of T\textsubscript{3} and T\textsubscript{4}. This effect is noted to occur within weeks of initiation of therapy and disappears 2 weeks after therapy has been discontinued.\textsuperscript{59} Glucocorticoids inhibit the entire hypothalamic–pituitary–thyroid axis and have a direct effect against thyroid hormone.\textsuperscript{19} The effects of phenobarbital are noted only in animals receiving long-term treatment. To produce reliable results, clinicians should not administer phenobarbital to patients for 4 weeks before thyroid function testing.\textsuperscript{18,63} Various studies\textsuperscript{18,65} have found the influence of NSAIDs to be variable, depending on the specific agent used. In animals that receive any of these medications, evaluation of thyroid function must be made with caution and preferably after they have stopped receiving the medications well in advance.

Another factor well documented to result in lower thyroid hormone levels is athletic conditioning and training. Several studies\textsuperscript{66–70} have demonstrated that well-conditioned sled dogs and greyhounds reliably have lower total and free T\textsubscript{4} levels, which may lead to misdiagnosis of hypothyroidism. In addition, recent vaccination has been demonstrated to cause a transient increase in circulating autoantibody levels. This may cause a truly hypothyroid animal to appear euthyroid and may result in a delay or discontinuation of appropriate therapy. Thyroid function testing should not be conducted if a patient has been vaccinated within the previous 2 weeks.\textsuperscript{13}

**TREATMENT AND THERAPEUTIC MONITORING**

Synthetic thyroid hormone supplementation easily treats hypothyroidism. Levothyroxine sodium is available as both human and veterinary products. It is recommended to avoid generic forms of the drug because human studies have demonstrated wide variability in the bioavailability of generic forms.\textsuperscript{2,71} If a generic form is used, it is important to always prescribe the same formulation to an individual patient. Hormone supplementation is usually initiated at 0.02 mg/kg PO q12h. Thyroid function testing is recommended 6 weeks after therapy has begun. The total T\textsubscript{4} level should be monitored and timed so that blood is taken 6 hours after pill administration.\textsuperscript{1,72} In stable, well-controlled animals, the total treatment may be given once daily with excellent clinical results, as long as adequate peak hormone concentrations

<table>
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<tr>
<th>Table 2. Comparison of Canine Thyroid Diagnostic Tests</th>
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<tr>
<td>Study</td>
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<tr>
<td>Peterson et al\textsuperscript{46}</td>
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<td>Dixon and Mooney\textsuperscript{47}</td>
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*ED = by equilibrium dialysis.*

**Factors Affecting Thyroid Function Test Results**

**Decreased thyroid hormone levels**
- Drugs: sulfonamides, glucocorticoids, phenobarbital, clomipramine, NSAIDs
- Good conditioning: racing greyhounds, sled dogs
- Other illness

**Increased thyroid hormone levels**
- Recent vaccination
- Presence of antithyroglobulin antibodies
are achieved. In animals that receive supplementation once daily, blood should be taken immediately before the medication is given and then again 6 hours later. When therapy is appropriate, the total T₄ level should be high normal to high. If the total T₄ level is significantly above normal, the medication dose should be decreased or the frequency changed. If the total T₄ level is low, an increase in the dose may be necessary. Before increasing the dose, the clinician must assess client compliance, ensure that no gastrointestinal issues will impact absorption, and confirm that there has not been a switch in the levothyroxine formulation. Supplementation levels can be increased to a maximum of 0.8 mg per dog per treatment. It should be noted that levothyroxine doses for dogs exceed those for humans and may confuse pharmacists or endocrinologists.

Thyroid function should be monitored every 6 to 8 weeks for the first 6 to 8 months of treatment and then once or twice yearly. Evaluation of TSH is a controversial tool to help assess response to therapy. In a well-controlled animal, the TSH level would be expected to be in the normal range. However, there is a report indicating that the TSH level may be normal in as many as 75% of dogs requiring an increase in their supplementation levels. An increased TSH level is a predictable indicator of the need to increase supplementation levels to achieve adequate hormone control. However, a normal TSH level alone does not indicate that hormone supplementation is adequate in all dogs.

An important aspect to help assess response to therapy is the degree to which clinical signs of hypothyroidism resolve. Marked improvement in the patient’s attitude, activity level, and alertness should occur within 1 week of starting therapy. Polyneuropathy usually starts to improve quickly, but complete resolution may take several months. The hematocrit count and serum cholesterol level should gradually resolve in the first weeks of therapy. Dermatologic abnormalities improve slowly, with complete resolution usually taking up to 3 months. Response to treatment is a valuable tool to help determine the success of therapy but should not replace appropriate blood tests. Hypothyroidism can be easily and successfully controlled, and the prognosis for affected animals, when appropriately treated, is excellent.

**MYXEDEMA COMA**

Myxedema coma is a rare, life-threatening, extreme manifestation of severe hypothyroidism and is considered an endocrine emergency. The mortality rate in humans ranges from 15% to 60%. Myxedema coma is rare in animals, and much of what is known in veterinary medicine is based on a few case reports or is taken from human medicine. The development of myxedema coma requires a precipitating event that overwhelms normal homeostatic mechanisms. In humans, this is often an infection, whereas in animals, no single event has been repeatedly identified.

The common findings in patients with myxedema coma are changes in mental status, altered thermoregulation, and nonpitting skin edema. Mentation changes can range from altered alertness to coma. Coma does not always occur, and in humans, mental depression is the most common assessment of mental status. Edema, localizing in the brain, is responsible for the development of altered mentation. Hyponatremia can cause a further decrease in the neurologic status. Patients with myxedema coma are often hypothermic but not shivering. Thyroid hormone has a permissive effect on calcium ATPase. In the hypothyroid state, there is decreased activity of this enzyme, resulting in decreased ATP use. ATP is the powerhouse of the cell, and with decreased activity, there is decreased oxygen consumption and thus decreased heat generation. In addition, hypothalamic dysfunction, secondary to edema formation in the brain, may lead to alteration in the thermoregulatory set-point. These changes may result in a lower body temperature and reduced likelihood to shiver. Shivering can be stimulated by the hypothalamus or sympathetic nervous system. T₄ amplifies catecholamine function, helping to stimulate muscular activity associated with shivering; therefore, a reduced T₄ level blunts the ability to shiver. Hypothermia reduces platelet function, resulting in hepatic platelet sequestration and decreased enzymatic activity within the coagulation system.
Hypothyroidism is a common endocrine disease in dogs but is rare in cats. The most common forms of hypothyroidism are lymphocytic thyroiditis and idiopathic thyroid atrophy. The clinical signs of the disease are vague and can affect many body systems. Evaluation of the total T₄ level is considered an excellent screening test. Evaluation of the canine TSH level is a good confirmatory test and has a specificity of 98% when it is used in conjunction with evaluation of the total or free T₃ levels. Several factors may alter the results of thyroid function testing. The presence of anti-T₄ antibodies can falsely increase total T₄ levels and mask true hypothyroidism. Alternatively, many drugs and athletic conditioning, in some breeds, may decrease total T₄ levels while not being associated with a true hypothyroid state. Treatment of hypothyroidism is easily achieved with levothyroxine supplementation. Success of therapy must be assessed with close monitoring via thyroid function testing. With appropriate treatment, hypothyroidism can be well managed and have an excellent prognosis. A rare complication of severe hypothyroidism is myxedema coma. This condition is difficult to recognize but is associated with an altered mental state, hypothermia without shivering, and nonpitting skin edema. With aggressive supportive therapy and intravenous thyroid hormone replacement, this condition may be successfully treated, although the mortality rate remains high.

**CONCLUSION**

Hypothyroidism and Myxedema Coma

- Establish an airway.
- Ensure adequate ventilation.
- Administer intravenous fluids: 0.9% sodium chloride (20 ml/kg [initial bolus]). Reassess and continue intravenous fluids (2.5–7 ml/kg/hr). Select rate based on blood pressure, heart rhythm, heart rate, and respiratory rate.
- Administer levothyroxine at 5 µg/kg (0.005 mg/kg) IV q12h.
- Once the animal can swallow, start levothyroxine at 20 µg/kg (0.02 mg/kg) PO q12h. This dose can be started while still using intravenous levothyroxine to help achieve therapeutic blood levels.
- Use passive rewarming (via water blankets or forced-air devices). Continue until the temperature is low normal and can be maintained without support.

*The levothyroxine dose should be decreased by 50%–75% if there is preexisting heart disease.*

**REFERENCES**


January 2007

**CE**


73. thumbs up? a. 0% b. <1% c. 10% d. 99%


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**ARTICLE #1 CE TEST**

*This article qualifies for 2 contact hours of continuing education credit from the Auburn University College of Veterinary Medicine. Subscribers may purchase individual CE tests or sign up for our annual CE program. Those who wish to apply this credit to fulfill state relicensure requirements should consult their respective state authorities regarding the applicability of this program. CE subscribers can take CE tests online and get real-time scores at CompendiumVet.com.*

1. **Which organ/gland is not directly involved in thyroid hormone production and regulation?**
   - a. thyroid
   - b. hypothalamus
   - c. adrenal gland
   - d. pituitary

2. **Which stimulatory hormone is produced in the pituitary?**
   - a. TSH
   - b. TRH
   - c. $T_4$
   - d. $T_3$

3. **How much of the total $T_4$ is free (i.e., unbound to protein)?**
   - a. 0%
   - b. <1%
   - c. 10%
   - d. 99%

4. **Which are the major forms of acquired hypothyroidism in dogs and humans?**
   - a. neoplastic destruction of the thyroid and idiopathic thyroid atrophy
   - b. radioiodine treatment and infection of the thyroid
   - c. idiopathic thyroid atrophy and lymphocytic thyroiditis
   - d. idiopathic thyroid atrophy and iodine deficiency

5. **Which panel gives clinicians the most initial information to assess thyroid function?**
   - a. total $T_4$ and TSH
   - b. total $T_3$
   - c. total $T_3$, reverse $T_3$, and free $T_4$
   - d. total $T_4$ and antithyroglobulin antibodies
6. Which interpretation of the following thyroid function profile is correct?

<table>
<thead>
<tr>
<th>Total T₄ level</th>
<th>TSH level</th>
<th>Free T₄ level</th>
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<tbody>
<tr>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

a. euthyroid
b. unclear; retest the patient in 4 weeks
c. hypothyroid
d. secondary hypothyroidism (sick euthyroid)

7. A dog has been receiving levothyroxine supplementation at a dosage of 0.02 mg/kg PO q12h for 6 weeks. The thyroid function test results follow. (Blood was taken 6 hours after pill administration.)

<table>
<thead>
<tr>
<th>Total T₄ level</th>
<th>TSH level</th>
</tr>
</thead>
<tbody>
<tr>
<td>High normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

What should be the next treatment step?

a. Continue with the same treatment, and retest the patient in 6 to 8 weeks.
b. Decrease the levothyroxine dose to every 24 hours.
c. Increase the levothyroxine dose.
d. The dog is not hypothyroid. Stop all treatment.

8. Resolution of clinical signs is helpful in assessing response to therapy. Which typical clinical sign of hypothyroidism can take many months to completely resolve?

a. weakness
b. anemia
c. dermatologic abnormalities
d. lethargy

9. Which is not an immediate treatment of myxedema coma in dogs?

a. intravenous levothyroxine administration
b. airway establishment
c. intravenous fluid therapy with 0.9% sodium chloride
d. rapid resuscitation of hypothermia

10. Which is not a common clinical sign or laboratory finding of myxedema coma?

a. hyponatremia
b. altered mental status
c. nonpitting edema of the skin
d. tachycardia