

Diagnosis and Management of Hypothyroidism

David L. Panciera, DVM, MS, DACVIM

Virginia-Maryland Regional College of Veterinary Medicine

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Hypothyroidism is a common disease in dogs that has many clinical manifestations. Thyroid function is evaluated in a wide variety of clinical circumstances, including many where interfering factors may be present. Diagnosis of hypothyroidism relies on identification of compatible clinical signs, performance of appropriate thyroid function tests, proper interpretation of these tests including knowledge of factors affecting the tests, and documentation of response to treatment.

Clinical findings

Canine hypothyroidism most frequently occurs in middle-aged, pure-bred dogs, with golden retrievers, doberman pinschers, boxers, and other breed being predisposed. Cutaneous manifestations, including dry, scaly skin, seborrhea, dry hair coat, alopecia, and hyperpigmentation are the most common abnormalities. Alopecia frequently begins in areas of friction including the tail and neck. Pyoderma and recurrent otitis externa are sometimes present. Pruritus is not a sign of hypothyroidism. About 50% of hypothyroid dogs are overweight or moderately obese. Weakness and exercise intolerance due to decreased metabolic rate or neuromuscular dysfunction is present in about 20% of dogs.

Neurological manifestations are occasionally present. Peripheral neuropathy is diagnosed in 5-10% of hypothyroid dogs. Localized neuropathies usually cause peripheral vestibular signs or facial nerve paralysis. Thyroid function should always be evaluated in dogs with unexplained localized neuropathy. Generalized polyneuropathy is manifest as generalized weakness, ataxia, and hyporeflexia. Megaesophagus has been diagnosed in hypothyroid dogs, but hypothyroidism has not clearly been proven to cause megaesophagus. Esophageal dysfunction usually persists despite treatment of the hypothyroidism when the two disorders occur together, but significant improvement can occur. Remember that dogs with polyneuropathy due to a variety of causes and those with other diseases (including aspiration pneumonia secondary to megaesophagus) often have serum T4 concentrations below normal due to euthyroid sick syndrome and not hypothyroidism.

Central nervous system signs, including head tilt, paresis, circling, strabismus, nystagmus, facial nerve paralysis, and trigeminal nerve dysfunction occur occasionally. Signs of central vestibular disease seem to occur most commonly. These can be sudden in onset or may be slowly progressive or intermittent. They usually respond rapidly to treatment. The association of aggression and other behavioral problems with hypothyroidism remains to be proven.

Clinical signs of cardiac dysfunction are uncommon in hypothyroid dogs, but bradycardia, muffled heart sounds, and weak pulses are sometimes present. Low voltage R-wave amplitude is frequently present and hypothyroidism should be considered when this is present. Hypothyroidism only rarely causes dilated cardiomyopathy, but can contribute to myocardial dysfunction in dogs with concurrent cardiac disease.

Reproductive abnormalities are poorly documented, but female dogs with hypothyroidism may have infertility, prolonged anestrus, and shorten estrus. Inappropriate

galactorrhea can occur in intact females. Fertility in male dogs is not affected by hypothyroidism.

Myxedema stupor/coma is a rare and life-threatening manifestation of hypothyroidism. Dogs present obtunded, stuporous, or comatose, hypothermic without shivering, and have bradycardia, non-pitting edema, and hypotension. Hyponatremia, lipemia, hypercholesterolemia, hypoglycemia, and hypocapnea may be present. Rapid replacement of thyroid hormones, passive warming, judicious fluid therapy, and other supportive care is indicated.

Routine laboratory tests

Hypercholesterolemia is a common finding in hypothyroid dogs, being present in 75% of cases. Mild, nonregenerative anemia is present in approximately 25% of hypothyroid dogs. Occasionally, hyponatremia and elevated alkaline phosphatase, alanine aminotransferase, and creatine kinase activities are present.

Thyroid function tests

For routine cases of suspected hypothyroidism, serum concentrations of total T4 and thyrotropin (TSH) are recommended as a minimum. Decreased T4 and elevated TSH confirm the diagnosis of hypothyroidism, but do not occur in all cases. In the presence of nonthyroidal illness, uncommon clinical signs of hypothyroidism (megaesophagus, neuropathy), or when the dog is being treated with certain drugs, a serum free T4 (fT4) measured by equilibrium dialysis (ed) should be performed. The most complete and useful information about thyroid function is obtained when total T4, fT4ed, TSH, and T4 and T3 autoantibodies are measured.

Serum total T4

Serum T4 is a sensitive, but not specific test for the diagnosis of canine hypothyroidism. The vast majority of dogs with hypothyroidism have a serum T4 below normal, but some normal dogs and those with a variety of other problems may have a low serum T4. A serum T4 concentration below normal in a dog with classical clinical signs of hypothyroidism and no overt concurrent illness is sufficient for a tentative diagnosis of hypothyroidism and warrants a clinical trial of thyroid hormone supplementation. A diagnosis of hypothyroidism should not be made if the serum T4 concentration is above the low-normal portion of the reference range.

Autoantibodies to T4 occur in about 15% of hypothyroid dogs, and these antibodies may falsely increase the serum T4 concentration from below normal into or above the normal range. This may occur in up to 10% of hypothyroid dogs, so measurement of total T4 alone would not be effective in diagnosing these cases. Because dogs have a much lower normal range of T4 than humans, it is important to use a laboratory with an assay optimized for the normal range of T4 in dogs, as many human laboratories do not accurately measure serum T4 in the low-normal range of dogs.

Serum T3

Serum T3 concentration is an unreliable test for evaluation of thyroid function. Some studies indicate that as many as 90% of hypothyroid dogs have a normal serum T3 concentration. In addition, T3 is frequently decreased in dogs with nonthyroidal illness. Measurement of serum T3 is of little use in the dog.

Serum fT4

Thyroxine is highly (99.9%) protein bound in the circulation. Protein binding can be altered by many nonthyroidal illnesses and by certain drugs. Measurement of the unbound or free hormone can provide a more accurate assessment of thyroid function in these cases. The only proven accurate method of measuring fT4 is using an equilibrium dialysis technique. This assay is now widely available through veterinary diagnostic laboratories. It is, however, more

expensive and time consuming than total T4 assays. The sensitivity of fT4 is equivalent to or slightly better than total T4 in diagnosing hypothyroidism in routine cases. More importantly, fT4 is more specific, particularly when nonthyroidal factors that can influence total T4 are present. Free T4 is less affected by most nonthyroidal illness and drugs, but still can be altered in cases of moderate to severe illness. In addition, fT4 by equilibrium dialysis is not affected by the presence of T4 autoantibodies that will falsely elevate total T4. Measurement of fT4 by equilibrium dialysis should be performed when uncommon clinical signs of hypothyroidism are present, the dog is being treated with a drug that may affect thyroid function, when nonthyroidal illness is present, and if autoantibodies to T4 are detected. The author uses this test in routine cases as well.

Serum TSH

Primary hypothyroidism results in a decrease in T4 and thus decreased negative feedback on the pituitary gland. In response, the pituitary secretes more TSH and plasma TSH levels increase. In man, TSH is elevated prior to any decrease of T4 or fT4 outside the normal range. In the dog, TSH concentration is elevated in only 65-75% of cases of hypothyroidism, so it is not a very sensitive test. The combination of decreased total T4 or fT4 with an elevated serum TSH is diagnostic of hypothyroidism. Therefore, a normal TSH does not rule out hypothyroidism, but an elevated TSH combined with a low T4 provides a definitive diagnosis.

TSH response test

The TSH response test is considered the gold standard for diagnosis of hypothyroidism in the dog and cat. Administration of TSH causes secretion of thyroid hormones, particularly T4. This test is best reserved for use when a confounding factor (nonthyroidal illness, drug administration) is present that makes diagnosis using basal hormone concentrations difficult. To perform the TSH response test, obtain a blood sample for measurement of serum T4 before and 4 hours after IV administration of 100 µg human recombinant TSH. A serum T4 concentration > 30 nmol/L is considered normal. Most hypothyroid dogs have little if any increase in T4 following administration and typically have pre and post-TSH T4 concentrations < 20 nmol/L. Pharmaceutical grade bovine TSH is no longer available and human recombinant TSH is very costly, making the test impractical in most circumstances.

Autoantibodies

Antibodies against either T4 or T3 or both are sometimes present in dogs with lymphocytic thyroiditis. The presence of these antibodies does not indicate that the dog is hypothyroid, but suggest that autoimmune thyroid disease is present. These antibodies frequently cause false elevation of T4 or T3 concentrations that result in marked elevation of the hormones. This is an *in vitro* artifact, and does not cause hyperthyroidism. It is also important to realize that a lower titer of these antibodies can result in an elevation of T4 from below normal into the reference range, thus reducing the sensitivity of T4 for diagnosis of hypothyroidism. Autoantibodies to T4 are present in about 15% of hypothyroid dogs. Autoantibodies can also cause the measured T4 or T3 to concentration to be in the normal range in a hypothyroid dog. Some diagnostic laboratories (i.e. Michigan State University) routinely assay for thyroid hormone autoantibodies.

Dogs with autoimmune thyroiditis may have circulating antibodies to thyroglobulin, the primary protein in the colloid of the thyroid gland. This is not a test of thyroid function, but rather a marker for the presence of autoimmune thyroiditis. It is not known how many dogs with a positive antithyroglobulin antibody and normal thyroid function tests develop hypothyroidism

in the future. The presence of these antibodies in a dog with borderline hypothyroidism or discordant results between tests supports a diagnosis of hypothyroidism.

Therapeutic response

In addition making a diagnosis of hypothyroidism using standard laboratory testing, response to treatment can be used to confirm the diagnosis. Every animal treated for hypothyroidism should be monitored for a response. A positive response to adequate levothyroxine treatment is expected in every hypothyroid dog, but not all clinical abnormalities present may be due to hypothyroidism and not all signs of hypothyroidism resolve rapidly nor completely. It is not recommended to initiate treatment without performing thyroid function testing, but if this is to be done, the following protocol should provide the most accurate assessment of response to treatment. Obtain history and physical examination after treatment for 6-8 weeks of levothyroxine treatment (0.02 mg/kg q 12 h). If a positive response has occurred, treatment should be withdrawn and the dog re-examined in 4-6 weeks. A diagnosis of hypothyroidism is made when the clinical signs improve or resolve during treatment and reoccur after cessation of treatment. Other treatment should be avoided during this trial period.

Nonthyroidal factors affecting interpretation of thyroid function tests

Breeds

Certain breeds have normal ranges of thyroid hormones that are different from most other breeds. Few have been evaluated, but greyhounds have serum total T4 and fT4 concentrations that are considerably lower than most other breeds. Scottish deerhounds also have total T4 concentrations that are well below the mean concentration of dogs in general and other sighthounds may have similar findings. Alaskan sled dogs have serum T4, T3, and fT4 concentrations that are below the reference range of most pet dogs, particularly during periods of intense training or racing.

Nonthyroidal illness

Illness not involving the thyroid gland can alter thyroid function tests and has been labeled “nonthyroidal illness” or “euthyroid sick syndrome”. Any illness can alter thyroid function tests, causing a fairly consistent decrease in total T4 and T3 concentrations in proportion to the severity of illness. Serum TSH concentration is increased in 8-10% of dogs with nonthyroidal illness. Serum fT4 measured by equilibrium dialysis is less likely to be affected, but can be increased or decreased. However, in dogs with substantial nonthyroidal illness, the fT4 is likely to be decreased. It is recommended that testing of thyroid function be postponed until the nonthyroidal illness is resolved. If this is not possible, measurement of T4, TSH and fT4 are indicated.

Autoantibodies

As previously mentioned, autoantibodies to T4 and/or T3 are sometimes present in dogs with autoimmune thyroiditis and do not indicate that the dog is necessarily hypothyroid. If T4 autoantibodies are present, the serum total T4 concentration is not valid. In this case, fT4 by equilibrium dialysis will be effective in accurately measuring the fT4 concentration.

Drugs

The drugs that are known to commonly alter thyroid function tests are glucocorticoids, phenobarbital, sulfonamides, clomipramine, and aspirin. Glucocorticoids suppress total T4 and sometimes fT4 as well. Phenobarbital causes decreased total T4 and mild increases in TSH. Sulfonamides can induce overt primary hypothyroidism with clinical signs and thyroid function tests that support the diagnosis. All the changes are reversible when the medication is

discontinued. There are dozens of drugs that affect thyroid function and thyroid function tests in man, so many others likely affect the dog as well.

Recommendations for routine testing

I routinely use Michigan State University's canine thyroid diagnostic profile (premium), which includes T4, T3, fT4 by equilibrium dialysis, fT3, TSH, T4 and T3 autoantibodies, and antithyroglobulin antibodies, for diagnosis of hypothyroidism. However, a low serum T4 concentration performed by a reliable (not human) laboratory is sufficient for a tentative diagnosis in a dog with classical clinical signs of hypothyroidism, while a T4 well within the normal range essentially rules out hypothyroidism in the absence of autoantibodies. I would recommend measuring serum TSH concentration as well in all cases, because an elevated TSH combined with a decreased T4 is almost always associated with hypothyroidism. Serum fT4 by equilibrium dialysis is a bit more sensitive than total T4 for diagnosis of hypothyroidism, and is affected less than total T4 by mild to moderate nonthyroidal illness. It may be impossible to accurately assess thyroid function in dogs with nonthyroidal illness or those receiving certain drugs.

Treatment of hypothyroidism

Levothyroxine is the only hormone that appears necessary for treatment of hypothyroidism. The frequency of levothyroxine dosing is controversial, and the only study to closely evaluate the response to treatment showed that once daily treatment is adequate. However, some dogs seem to respond better to twice daily treatment and because response to treatment is an important part of confirming the diagnosis of hypothyroidism, I recommend an initial dosage of 0.02 mg/kg PO BID. I rarely exceed 0.8 mg BID as an initial dosage even in very large dogs. Most dogs show improvement within the first 1-2 weeks, with increased activity, improved attitude, partial or complete resolution of neurologic signs. The cutaneous manifestations of hypothyroidism may take several weeks to improve and months to resolve. Post-pill testing should be carried out in most cases, but clinical response is the most important monitoring tool. Peak T4 concentrations occur 4-6 hours after administration of levothyroxine and should be in the high normal to slightly above normal range (40-70 nmol/L). If measured, serum TSH concentrations should be in the normal range or undetectable. Once a good clinical response is obtained, treatment can be reduced to once per day in most cases. Hyperthyroidism is the most common complication of treatment with levothyroxine, but it is rare in dogs. Clinical signs are similar to those of hyperthyroidism in cats and the diagnosis is confirmed by documenting a substantial elevation of serum T4. Treatment consists of stopping levothyroxine treatment for 2-3 days, then instituting treatment at a lower dose.