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Testing the Endocrine System for Thyroid and Parathyroid Disorders: It Is All About Signaling Hormones!

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The endocrine system is complex and sometimes poorly understood. Although veterinary technicians are often involved with preparing and submitting endocrine tests and caring for patients with endocrinopathies, it may be difficult to understand what is happening in affected patients. This article unravels some of the mysteries of the endocrine system and highlights the need for testing to evaluate endocrine functions. A complete discussion of the endocrinopathies mentioned here is beyond the scope of this article. However, understanding endocrine testing can greatly enhance a technician's role in helping to manage endocrinopathies. The endocrine system comprises many glands and organs; this article focuses on testing the thyroid and parathyroid glands.

Thyroid Disorders: Hypothyroidism and Hyperthyroidism

The thyroid gland, pituitary, and hypothalamus form part of a feedback loop that helps the body regulate thyroid hormone levels. The hypothalamus secretes thyrotropin-releasing hormone, which stimulates the pituitary to release thyroid-stimulating hormone (TSH). TSH signals the thyroid gland to release thyroid hormones, with the major ones being triiodothyronine (T_3) and thyroxine (T_4).

Hypothyroidism

Hypothyroidism—low levels of circulating thyroid hormones—can cause clinical signs. Hypothyroidism is reportedly the most common canine endocrinopathy,[1] but it rarely affects cats. Hypothyroidism is typically caused by thyroid gland failure, in which the gland atrophies (or is attacked by the immune system), causing a decrease in T_3 and T_4 production. Rarely is hypothyroidism caused by a pituitary or hypothalamic condition. Clinical signs include lethargy, mental dullness, and alopecia (bilateral and nonpruritic) and may include recurrent skin infections, hypothermia, bradycardia, and myopathies or neuropathies.[1]

In patients suspected of having hypothyroidism, concentrations of the following hormones can be tested: total T_3, total T_4, free T_3, free T_4, TSH, and antithyroid autoantibody hormone. Because total and free T_3 concentrations are not typically used for diagnosing hypothyroidism, they have been excluded from this discussion.

The total T_4 concentration is typically used as a screening test, meaning that if the level is low, further testing is probably needed. Because the total T_4 concentration refers to both bound (to proteins) and unbound (biologically available) portions of the total amount of T_4, other factors can affect its measurement. Patients that are critically ill or undergoing certain drug therapies can have a low total T_4 concentration but a normal biologically active free T_4 concentration; this is called *euthyroid sick syndrome*. Thus, if a patient has a low total T_4 concentration on routine blood work, follow-up tests should be performed. A patient with a low total T_4 concentration, apparent or nonapparent concurrent disease, and a normal free T_4 concentration may have euthyroid sick syndrome.

A low free T_4 level correlates highly with clinical illness,[1] but the free T_4 level should be measured only by equilibrium dialysis, which is more accurate for detecting hypothyroidism than the total T_4 test.[1]

The TSH level can also be measured. If the thyroid gland is not functioning properly and circulating thyroid hormone levels are low, the TSH level should be high. However, the accuracy of the TSH assay for diagnosing hypothyroidism is quite low. Although the TSH level would be expected to be high if hypothyroidism is present, it can often be high, low, or normal. Therefore, hypothyroidism should not be diagnosed based on a TSH level alone, and errors may occur when the free T_4 and TSH levels are interpreted together as a unit; however, a low free T_4 level combined with a high TSH level is highly predictive of hypothyroidism. For example, a patient with a low free T_4 level and a normal TSH level may not be considered to have hypothyroidism if the TSH level is taken at face value.

Patients with an autoimmune component to hypothyroidism (autoimmune thyroiditis) can have elevated levels of thyroid hormone antibodies, which can be measured as a high thyroglobulin autoantibody titer. An elevated T_3 or T_4 autoantibody titer results

Table 1. Test Results for Hyperthyroidism, Hypothyroidism, and Sick Euthyroid Syndrome

	T3 Level	Total T4 Level	Free T4 Level	TSH Level	Autoantibodies
Hyperthyroidism	NA	Elevated or normal	Elevated		
Hypothyroidism	NA	Decreased or normal	Decreased	Normal to increased	Present if there is lymphocytic thyroiditis
Sick euthyroid syndrome	NA	Decreased or normal	Normal	Normal	Not present

in a high thyroglobulin autoantibody titer.[1] Because antibodies can cross-react, the total T_4 level may be normal to slightly low if antibodies are present, but the free T_4 level determined by equilibrium dialysis will be significantly low.[1] However, antibody levels are not routinely measured because the presence of thyroglobulin autoantibodies does not change the approach to treatment.

Hyperthyroidism

Hyperthyroidism is common in cats but rare in dogs. Affected patients often have cachexia, hyperactivity, polyuria, polydipsia, polyphagia, hypertension, tachycardia, and thyroid "slip"—a palpable thyroid nodule that is typically a benign adenoma; however, adenocarcinoma is possible. These neoplasms increase production of thyroid hormones. Most hyperthyroid cats have an elevated total T_4 level; however, this level may be in the middle to high range of normal in some cats (an average of ~33.5% of subjects in one study[2] of more than 900 cats). Therefore, testing the total T_4 level is somewhat useful for screening, but additional testing is often required to confirm clinical suspicion.[2] As in dogs, testing the free T_4 level can confirm a normal (within reference range) total T_4 level in cats. In one study,[2] more than 98% of hyperthyroid cats had an elevated free T_4 level. Therefore, in cats, hyperthyroidism is generally diagnosed based on either an elevated serum total T_4 level or a "normal" total T_4 level and an elevated free T_4 level.[2] **TABLE 1** summarizes the test results for hyperthyroidism, hypothyroidism, and sick euthyroid syndrome.

Parathyroid Disorders: Hypoparathyroidism and Hyperparathyroidism

The parathyroid hormone regulatory system can also be deranged in disease. The four parathyroid glands are located above the thyroid gland in the neck; two parathyroid glands reside on each cranial pole of the thyroid gland. These glands are responsible for secreting parathyroid hormone (PTH), which is the primary regulator of the calcium level in the body.

PTH regulates calcium in the following ways[3]:

- PTH increases resorption of calcium and phosphorus in the renal tubules
- PTH stimulates conversion of inactive vitamin D (cholecalciferol) to active 1,25-dihydrocholecalciferol, increasing calcium absorption by the intestines
- PTH increases osteoclast activity in bone, enhancing resorption of calcium and phosphorus

Vitamin D is absorbed in the small intestine and has multiple functions. It stimulates bone and kidney resorption of calcium and phosphorus, although these effects are minor compared with its gastrointestinal (GI) effects. Renal 1α-hydroxylase is required for the final step in converting the absorbed inactive metabolite form of vitamin D (cholecalciferol) to its active form (1,25-dihydrocholecalciferol). Calcitonin is produced in the thyroid gland, secreted as the calcium level rises, and blocks bone and renal resorption of calcium.[3]

Hypoparathyroidism

The pathophysiology of hypoparathyroidism is poorly understood. Iatrogenic causes are the best described, based on observation of the results of unintended parathyroidectomy during a thyroidectomy; however, immune-mediated and congenital causes have been proposed.[3] The most common cause is idiopathic in dogs and iatrogenic in cats.[3]

Patients with primary hypoparathyroidism exhibit hypocalcemia due to urinary loss of calcium and decreased absorption of calcium in the GI tract,[3] hyperphosphatemia (PTH tries to elevate the calcium level, stimulating phosphorus retention), normal renal function, and an inappropriately low PTH level. Clinical signs include weakness, lethargy, twitching, ataxia, and disorientation; polyuria, polydipsia, vomiting, and diarrhea are less common.[3] A hypocalcemic patient should have an elevated PTH level; therefore, an inappropriately low PTH level in conjunction with hypocalcemia is considered diagnostic of hypoparathyroidism. Calcium and PTH levels should be measured together to document an inappropriately low PTH level along with hypocalcemia.

To diagnose hypoparathyroidism, the ionized calcium, phosphorus, and PTH levels should be tested. Diagnostic differentials for a patient with hypocalcemia include eclampsia (puerperal tetany), acute pancreatitis, renal failure, hypoalbuminemia, ethylene glycol toxicosis, laboratory error (use of EDTA), and hypomagnesemia.[3]

Hyperparathyroidism

Hyperparathyroidism is often due to a neoplastic process, such as a parathyroid adenoma or carcinoma. However, hyperparathyroidism can be due to hypertrophy of parathyroid chief cells, which can be overstimulated due to low calcium and/or phosphorus levels. Renal secondary hyperparathyroidism can potentiate this. However, in primary hyperparathyroidism, the most common clinicopathologic finding is hypercalcemia.[4]

Table 2. Diagnostic Differentials for Hypercalcemia

	Total Calcium Level	Ionized Calcium Level	Phosphorus Concentration	PTH Level	PTH-Related Protein Level	Vitamin D Level
Granulomatous condition	Elevated	Elevated	Normal to elevated	Low normal to Low	Nonexistent	Low normal[5]
Orthopedic	Elevated	Elevated	Elevated	Low	Nonexistent	Normal
Spurious	Mildly elevated	Mildly elevated	Normal	Normal	Nonexistent	Normal
Hyperparathyroidism	Elevated	Elevated	Normal to low	Elevated	Nonexistent	Normal
Vitamin D toxicosis	Elevated	Elevated	Normal to elevated	Normal to low	Nonexistent	Elevated
Addison disease	Elevated	Typically normal	Normal or elevated	Normal	Nonexistent	Normal
Renal disease	Normal or elevated	Normal to low	Normal or elevated	Normal to elevated	Nonexistent	Normal
Neoplasia	Elevated	Elevated	Normal to low	Normal to low	Elevated	Normal
Idiopathic	Elevated	Elevated	Normal	Normal	Nonexistent	Normal
Temperature (hypothermia)	Elevated	Elevated	Normal	Low	Nonexistent	Normal

Renal secondary hyperparathyroidism occurs in some cases of chronic renal disease. The loss of nephron function results in several mechanisms that lower the ionized calcium level. This chronically stimulates PTH secretion, causing hypertrophy of the parathyroid chief cells.

Hypercalcemia is a consistent finding in hyperparathyroidism, regardless of the cause, and is often found through routine blood work. The mnemonic *GOSH DARN IT* can be used to remember the diagnostic differentials associated with hypercalcemia: *G*ranulomatous (e.g., fungal infection), *O*rthopedic (e.g., osteosarcoma, osteomyelitis), *S*purious (e.g., laboratory error), *H*yperparathyroidism; vitamin *D* toxicosis (e.g., due to cholecalciferol rodenticides), *A*ddison disease, *R*enal disease, *N*eoplasia (e.g., PTH-related protein release); *I*diopathic, *T*emperature (e.g., hypothermia may cause hypercalcemia).[3] Patients with hypercalcemia unrelated to hyperactive parathyroid glands should have a low PTH level in the presence of an elevated calcium level. A total calcium test—which tests protein-bound, ionized, and complexed calcium levels—is often performed in biochemical panels. The total calcium level may be the first parameter that is elevated, signaling hypercalcemia. Additional testing may include the levels of ionized calcium (the biologically active form of calcium in the blood), PTH, PTH-related protein, and vitamin D. Diagnosis of hyperparathyroidism is based on high ionized calcium, low or low-normal phosphorus, and elevated PTH levels.[4] Results of the tests discussed above are summarized in **TABLE 2** to help differentiate between the various causes of hypercalcemia.

Conclusion

The endocrine system is highly complex, so critical thinking is necessary to understand test results. Concentrations of hormones and other components in serum are the result of multiple influences and feedback mechanisms. For veterinary technicians, a basic understanding of how to interpret endocrine test results is essential for caring for small animals.

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1. **Which of the following parameters is often used as a "screening" test for hyperthyroidism?**
   - **a.** free T_4
   - **b.** TSH
   - **c.** corticotropin
   - **d.** total T_4

2. **Which parameter(s) can help diagnose hypothyroidism?**
   - **a.** free and total T_4 levels
   - **b.** TSH level
   - **c.** T_4 autoantibody level
   - **d.** all of the above

3. **Which test(s) is/are most often used to confirm a suspicious case of hypothyroidism that was not diagnosed based on a total T_4 level?**
   - **a.** corticotropin stimulation test
   - **b.** T_3, free T_4, and TSH level tests
   - **c.** free T_4, TSH, and T_4 autoantibody level tests
   - **d.** T_3 and reverse T_3 level tests

4. **Which of the following describes the major diagnostic differentials for hypercalcemia?**
   - **a.** granulomatous, orthopedic, spurious, hyperparathyroidism, vitamin D toxicosis, Addison disease, renal disease, neoplasia, idiopathic, temperature
   - **b.** granulomatous, osteopathic, spurious, hypercalcemia, vitamin D toxicosis, Addison disease, renal disease, neoplasia, idiopathic, temperature
   - **c.** granulocytic, orthopedic, spurious, hyperparathyroidism, vitamin D toxicosis, vitamin A toxicosis, renal disease, neoplasia, idiopathic, temperature
   - **d.** granulomatous, osteosarcoma, spurious, hypoparathyroidism, vitamin D toxicosis, Addison disease, renal disease, neoplasia, idiopathic, temperature

5. **In patients with idiopathic hypercalcemia, what is the PTH level?**
   - **a.** normal
   - **b.** elevated
   - **c.** decreased
   - **d.** nonexistent

6. **Hypocalcemia and a low PTH level indicate**
   - **a.** hyperparathyroidism.
   - **b.** hypoparathyroidism.
   - **c.** vitamin D toxicosis.
   - **d.** granulomatous disease.

7. **What is/are the major function(s) of calcitonin?**
   - **a.** conversion of calcium into bone
   - **b.** excretion of calcium
   - **c.** to decrease the blood calcium level
   - **d.** none of the above

8. **If a patient has hypercalcemia due to a cause unrelated to the parathyroid gland, the PTH level would be expected to be**
   - **a.** high.
   - **b.** low.
   - **c.** normal.
   - **d.** none of the above

9. **How do antithyroid antibodies affect thyroid hormone tests?**
   - **a.** The antibodies do not have an effect.
   - **b.** The antibodies can cross-react, causing the results of thyroid hormone tests to be falsely elevated.
   - **c.** The antibodies can cross-react, causing the results of thyroid hormone tests to be falsely decreased.
   - **d.** none of the above

10. **What are the common clinical signs of hyperthyroidism?**
    - **a.** lethargy, weight gain, and vomiting
    - **b.** hyperactivity, tachycardia, polyuria, polydipsia, and polyphagia
    - **c.** weakness, collapse, and seizures
    - **d.** none of the above