# Endocrinology 101 for Dermatology

**Catherine A. Outerbridge**
Department of Veterinary Medicine and Epidemiology, School of Veterinary Medicine
University of California, Davis, Davis, CA, USA

## Introduction

Those endocrine diseases that cause decreases in thyroid hormone, increases in cortisol, or sex steroid hormone imbalances are excellent examples of dermatologic manifestations of systemic disease. That said, the dermatologist may be the clinician that is recognizing cutaneous clues that necessitate the need to evaluate for endocrinopathies that can cause these hormonal disturbances.

## Hypothyroidism

The true prevalence of canine hypothyroidism is not known, yet it is often described in many textbooks as the most commonly diagnosed endocrine disorder in the dog. Spontaneous hypothyroidism is a rare disease in the cat. Many dogs that are placed on thyroid replacement therapy with the diagnosis of hypothyroidism are in all likelihood not truly hypothyroid. This in part results from the fact that no one test is optimal, that drugs and concurrent illness can alter test results, and that the clinical signs of hypothyroidism can be vague and involve almost any organ system. So attaining the correct diagnosis can be challenging and hypothyroidism is often incorrectly deemed the cause for many presenting complaints. Making the diagnosis should be based on the presence of supportive clinical signs in the patient whose routine lab work does not reveal any other significant disease and evaluation of the thyroid gland function documents in adequate production of thyroid hormone.

### Pathogenesis

Thyroid hormone deficiency can occur if there is dysfunction at any point in the hypothalamic - pituitary-thyroid gland axis. Over 95 % of cases of canine hypothyroidism are the result of dysfunction of the thyroid gland itself. The causes of primary acquired hypothyroidism in the adult dog, based on histologic evaluation of thyroid gland biopsies, are equally divided between lymphocytic thyroiditis and idiopathic atrophy of the thyroid gland. Idiopathic atrophy of the thyroid gland may represent the end stage of lymphocytic thyroiditis. Lymphocytic thyroiditis is a slowly progressive disease and development of obvious signs of hypothyroidism will not occur until at least 75% of the function of the thyroid gland is lost. Certain breeds and dog leukocyte antigen (DLA) haplotypes are associated with increased risk for development of hypothyroidism. These breeds include the Doberman pinscher, Giant Schnauzer, Rhodesian ridgeback and the English setter. Hypothyroidism can affect mixed breed and purebred dogs and the disease is more common in the Akita, Doberman Pinscher, Beagle, and Golden Retriever. Neoplastic destruction of thyroid tissue can be a rare cause of primary hypothyroidism, as can iodine deficiency, congenital hypothyroidism, treatment with radioactive iodine and certain drug therapies (potentiated sulfonamides).

Less than 5% of dogs with hypothyroidism have problems with the function of the pituitary gland to secrete thyrotropin (TSH) with resultant secondary follicular thyroid atrophy (secondary hypothyroidism) or problems with the hypothalamus to secrete thyrotropin-releasing hormone (TRH) (tertiary hypothyroidism). Reported causes of secondary hypothyroidism include pituitary tumors, congenital pituitary malformations (cystic Rathke's pouch), pituitary trauma or surgery.

Thyroid Hormone Physiology

Thyroid hormone regulation is a complex process that involves the hypothalamus, pituitary gland, thyroid gland, plasma transport proteins and the cellular uptake and metabolism of the thyroid hormones. Understanding physiology and regulation can help clinicians better interpret test results. Thyrotropin - releasing hormone (TRH) is produced by the hypothalamus, stimulates the secretion of TSH by the pituitary, and increases the bioactivity of TSH. TSH stimulates the synthesis and release of thyroxine (T4) and 3,5,3'-triiodothyronine (T3). The thyroid hormones once released have a negative feedback on the pituitary and hypothalamus to decrease both TSH and TRH secretion. TSH secretion also decreases because of somatostatin, dopamine, catecholamine, TNFα and some interleukins.

Once in circulation thyroid hormones are tightly bound to plasma transport proteins. In dogs, protein binding of T4 is weaker than in humans and consequently dogs have lower serum total T4 levels and higher free T4 levels than are documented in humans. Only the unbound hormone is "free" or available to enter cells via either passive diffusion or receptor mediated active transport. Once within the cell T3 binds to nuclear receptors, initiating the actions of thyroid hormone on cellular protein synthesis. Thyroxine (T4) must undergo deiodination to T3 to be able to bind to the cell's nuclear thyroid receptor. About 40% to 60% of T3 in the dog is derived from extra-thyroidal deiodination of T4 in peripheral tissues. Therefore, T4, although it has some intrinsic activity, is often considered a prohormone requiring deiodination to T3 to exert the metabolic effects of thyroid hormone. Thyroxine can also undergo deiodination to form the metabolically inactive reverse T3 (3, 3', 5'-triiodothyronine). This deiodination pathway increases during periods of nonthyroidal illness (NTI).

Clinical Signs

The clinical signs of hypothyroidism are varied and often vague and insidious in their onset. Thyroid hormones influence protein synthesis in most tissues and consequently the function of many organ systems can be altered in hypothyroidism. The most common clinical signs are referable to changes in overall metabolic rate and the appearance of the skin. These signs include lethargy, weight gain, exercise intolerance, alopecia, changes in coat quality and disturbances in cornification. Some clinical signs reportedly associated with hypothyroidism may result from breed predispositions to both hypothyroidism and other disorders rather than a cause and effect due to hypothyroidism. Less common clinical signs reportedly associated with hypothyroidism but known to be associated with this endocrinopathy include muscle weakness from myopathy or peripheral neuropathies, CNS signs associated with myxedema, prolonged anestrus, prolonged parturition & increased periparturient mortality of pups, and corneal lipid accumulation.

*Dermatologic Signs:* Thyroid hormones are very important to the skin and promote the initiation of the anagen phase of the hair follicle cycle. Consequently, many hypothyroid dogs have some degree of alopecia, often first noticeable in areas or wear (neck in the region of the collar, tail, dorsal muzzle, pressure points, lateral trunk). The extent and pattern of alopecia can vary between breeds of dogs and individual animals. For example, Rhodesian Ridgebacks can develop an unusual striping pattern of alopecia. Hypothyroidism causes an increase in the number of hair follicles in telogen so clinically the hair coat often appears dry, dull or may be faded in color, and there may be failure to regrow hair in areas that have been clipped. Hypothyroidism results in disturbances in cornification that will clinically present with scaling and pinnal margin seborrhea may be seen in some dogs. There can be variable hyperpigmentation, and accumulation of glycosaminoglycan in the dermis resulting in facial myxedema that gives the "tragic look" of hypothyroidism. The normal barrier function of the epidermis is likely impaired in hypothyroid animals and in animal models, impaired neutrophil and lymphocyte function

has been reported. Consequently, recurrent pyoderma and otitis externa can occur in hypothyroid animals. In some cases, recurrent or refractory otitis externa or recurrent pyoderma may be the only presenting clinical signs in a dog with hypothyroidism.

Feline Hypothyroidism

Spontaneous hypothyroidism in cats is rare. One reported case had similar clinical signs to dogs with a dull dry, hair coat that was lighter in color than normal and the cat had a puffy face. However, experimentally thyroidectomized cats did not; they reportedly groomed less, developed matting and seborrhea but only focal alopecia on pinnae and pressure points. A recent study identified seven cats with spontaneous hypothyroidism with six having bilateral goiter and four with hair coat changes. Cats can acquire hypothyroidism as a sequela of treating hyperthyroidism with radioactive iodine or complete thyroidectomy.

Diagnosis of Canine Hypothyroidism

*Clinicopathologic Findings:* If there is clinical evidence to make the clinician suspicious of the diagnosis of hypothyroidism then a complete blood cell count, (CBC), serum biochemistry panel and serum T4 level should be performed. The documentation of a mild, normocytic, normochromic anemia and fasting hypercholesterolemia will add evidence for the suspicion of hypothyroidism. These tests are equally important to evaluate for any evidence for non-thyroidal illness (NTI). NTI and certain medications (corticosteroids, phenobarbital, sulfa antibiotics, some NSAIDs) can influence thyroid levels and complicate the interpretation of thyroid tests and the correct diagnosis of hypothyroidism. Dogs with moderate or severe NTI, including dogs with hyperadrenocorticism, will have total T4 decreased below normal range. Thyroid testing of sick dogs, or dogs receiving medications known to alter thyroid hormone test values should be delayed until the non-thyroidal illness can be resolved. Drugs known to alter thyroid values should be discontinued for several weeks prior to obtaining tests to evaluate thyroid function.

*Thyroid Function Tests* There are a number of different tests that can be considered when evaluating thyroid function but the most commonly used are baseline total thyroxine, (T4), endogenous TSH, free thyroxine (fT4) and thyroglobulin autoantibodies (TGAA). A challenge in interpretations is that there are a number of factors that can influence measurable concentrations of thyroid hormones. These include age, breed, sex hormone levels, athletic training of the dog, NTI and a variety of drugs (see factors affecting thyroid testing below).

*Serum Total Thyroxine (T4) Concentrations:* Total thyroxine (T4) levels will be low in dogs with hypothyroidism. A single determination of serum total T4 concentration can be used as a screening test but is most useful if the value is greater than 2 mg/dl as this will eliminate or "rule-out" the diagnosis of hypothyroidism. Dogs with low or low normal T4 levels with supportive clinical signs of hypothyroidism disease (with no evidence for NTI and no drug history to influence T4 values) need to undergo further testing to confirm the diagnosis. A thyroid panel, which includes TSH and fT4, is the most common next diagnostic evaluation to pursue. It is critical to remember that depending on the severity of concurrent NTI euthyroid dogs may have extremely low serum levels of T4. Older dogs and sight hounds (any age) have lower T4 concentrations. Numerous drugs can change T4 values.

*Serum Total T3 Concentrations*: Although T3 is the most important biologically active thyroid hormone at a cellular level, a large portion of it is produced by deiodination in peripheral tissues. It is therefore

not the predominant circulating hormone produced by the thyroid gland and T3 measurements are unreliable when used to evaluate thyroid gland function. It is not considered a sensitive or specific test for diagnosing canine hypothyroidism.

*Free Thyroxine* ***(fT4):*** Free T4 (fT4) is the biologically active form of thyroxine. It regulates pituitary production of TSH. The fT4 fraction of thyroid hormone is less influenced by NTI and drug therapy than total T4 concentrations. However, it can be decreased by glucocorticoids, long-term anticonvulsants and trimethoprim-potentiated sulphonamides. Commercial assays that measure fT4 by radioimmunoassay are less accurate in dogs. Using an equilibrium dialysis assay, fT4 concentrations measurements are more accurate and this is the preferred method to measure fT4 in the dog. The sensitivity of measuring fT4 to diagnose hypothyroidism has been reported to be 80 to 98% and the specificity has been reported to be between 92 to 98%.

*Endogenous canine TSH:* In humans, hypothyroidism and hyperthyroidism are accurately diagnosed using sensitive assays for endogenous TSH. TSH is a species-specific hormone and until 1997, a commercial assay for measuring endogenous canine TSH (cTSH) had not been validated. TSH should be elevated in hypothyroid animals but it is not consistently increased in canine hypothyroidism and up to 38% of hypothyroid dogs may have a cTSH concentration within the reference range. TSH can also be elevated in some dogs with NTI and inappropriate elevations of cTSH have been documented in 18% of thyroid dogs. The use of cTSH as a screening test is questionable since the sensitivity is low, it does however have good specificity. It should not be used alone but it does increase the specificity of fT4 measurements. Measuring the cTSH response to TRH administration did not improve the accuracy of diagnosing hypothyroidism.

*Free Thyroxine (fT4) and Endogenous TSH Serum Concentrations:* The test of choice to confirm the diagnosis of hypothyroidism is to concurrently measure the serum concentration of endogenous canine TSH and free T4 concentrations (measured by equilibrium dialysis). Used together these two tests have a reported accuracy of 86%, a sensitivity of 74 to 80 % and a specificity of 98%. An elevated cTSH serum level and a decreased fT4 concentration are consistent with hypothyroidism.

*TSH Stimulation Testing:* This test used to be the gold standard for the diagnosis if hypothyroidism. It evaluates thyroid gland reserve and is used in dogs with low T4 to differentiate hypothyroidism from NTI. Human recombinant TSH can be used in dogs to perform a TSH response test to evaluate for hypothyroidism. However, the human recombinant TSH, Thyrogen (Genzyme Corporation, Cambridge, ME) is very expensive. After reconstitution, if doses are kept in the freezer it will provide TSH for 7 to 15 tests depending on the dose used. Serum T4 levels are measured before and 6 hours after intravenous administration of 75 to 150 micrograms of human recombinant TSH. Hypothyroidism is confirmed if the baseline and post stimulation T4 samples are below reference range.

*Measurements of Anti-Thyroglobulin, Anti-T4 and Anti-T3 Antibodies:* Antibodies to thyroglobulin, T4 and T3 can develop in lymphocytic thyroiditis. Anti-thyroglobulin antibodies were detected in 59% of hypothyroid dogs in one study. Dogs with positive anti-thyroglobulin antibodies but normal thyroid function do not require therapy but should be monitored for future development of hypothyroidism. Antibodies to T3 occur more commonly than anti-T4 antibodies and can interfere with some assays used to measure T3 or T4, resulting in an erroneously high value. When serum T3 or T4 values are elevated

and do not correlate with the clinical presentation, evaluating for the presence of antibodies against T3 or T4 can help determine if there is interference with the assay.

Factors Affecting Thyroid Function Testing

*Nonthyroidal Illness:* Nonthyroidal illness can be caused by systemic illness (neoplasia, diabetic ketoacidosis, renal or hepatic disease, heart failure or severe inflammatory disease), surgery or trauma. NTI influences thyroid physiology and complicate the interpretation of thyroid tests and therefore the diagnosis of hypothyroidism. Studies have shown that 60% of euthyroid dogs with severe illness will have low serum total T4 concentrations. Reductions in serum total T4 concentrations in severe illness correlate with a higher mortality rate. Reductions of thyroid hormones in NTI may serve a protective role against the catabolic effects of illness and it is not considered appropriate to supplement these patients with thyroid hormones. Possible mechanisms for the reduction in serum total T4 seen in dogs with NTI include impaired binding to, reduced concentrations of, or reduced affinity for plasma carrier proteins. Decreases in TRH or TSH secretion resulting in decreased T4 production and possible direct effects on the thyroid gland suppressing T4 production are suspected to occur in NTI including hyperadrenocorticism. In dogs with severe NTI serum total T4 is typically decreased, free T4 may be normal but can be decreased in some cases, and serum T3 concentrations are often low. TSH concentrations may occasionally be increased but are usually normal. Even the response to TSH stimulation can be blunted in NTI making the distinction between hypothyroidism and NTI difficult. The most accurate method to evaluate for hypothyroidism in a dog with concurrent severe NTI is to resolve the nonthyroidal illness and then assess thyroid function

*Effects of Drugs on Thyroid Tests:* Glucocorticoids, phenobarbitol and trimethoprim potentiated sulphonamide antibiotics are known to influence thyroid function tests. The effect of glucocorticoids on thyroid function testing is in part dosage dependent. Immuno-suppressive dosages of glucocorticoids produce greater suppression than anti-inflammatory dosages. Duration of therapy with glucocorticoids may also influence the degree of change to thyroid function. It is recommended that dogs not receive glucocorticoids for at least 4 weeks prior to evaluating thyroid function. Dogs receiving high doses for long periods of time may need longer withdrawal times. Dogs receiving phenobarbital have been documented to have decreased tT4 and decreased fT4 concentrations. Endogenous TSH was increased in one study compared to untreated epileptic dogs but was not significantly changed in another study evaluating the effects of anticonvulsants on thyroid function. Sulfa antibiotics can depress T4 secretion from the thyroid glands and cause functional hypothyroidism and consequently negative feedback to the pituitary gland is lost so endogenous TSH increases.

| Drugs | Total T4 | Free T4 | Endogenous TSH |
|---|---|---|---|
| Glucocorticoids | ↓ or NC | ↓ or NC | NC or ↓ |
| Phenobarbital | ↓ or NC | ↓ or NC | NC or ↓ |
| Sulfonamides | ↓ | ↓ | ↑ |
| Potassium Bromide | NC | NC | NC |
| Clomipramine | ↓ | ↓ | NC |
| Aspirin | ↓ | NC | NC |
| Ketoprofen | ↓ | NC | NC |
| Carprofen | ↓ or NC | ↓ or NC | ↓ or NC |
| | | | |
| Nonthyroidal illness | ↓ | ↓ or NC | NC or ↑(slight) |

**NC= no change**

Therapeutic Trials with Levothyroxine

If the clinical suspicion of hypothyroidism is high and the diagnostic screening tests are equivocal it has been advocated to treat without a definitive diagnosis. This is in part because there is minimal risk to supplementing a normal dog with levothyroxine and the medication is relatively inexpensive. Thyroid hormone therapy is a signal for hair follicles to initiate anagen so hair regrowth may occur even in a dog with NTI. To confirm that a dog's clinical signs were caused by hypothyroidism versus thyroid hormone responsive change, after there has been a positive response to therapy thyroid supplementation should be stopped and clinical signs should return.

It is important to remember that once levothyroxine is administered to a normal dog the pituitary will stop secretion of TSH because of negative feedback from the exogenous source of thyroid hormone. This will result in atrophy of the thyroid glands. To be able to evaluate thyroid function after initiation of thyroid supplementation, levothyroxine must be discontinued for at least 6 to 8 weeks. An incorrect diagnosis of hypothyroidism can be costly as therapy is life long and it could also mean the delay in diagnosing another disease.

Treatment and Monitoring

Levothyroxine administration (0.01-0.02 mg/kg orally twice daily) is required lifelong therapy to manage canine hypothyroidism. Some dogs can be managed with once a day therapy (0.02 to 0.04 mg/kg), with a maximum initial dose of 0.8 mg. Ideally, dogs should receive the same brand of replacement thyroid hormone. There can be differences in the clinical response of dogs when receiving different manufactured sources of thyroid supplementation. Iatrogenic hyperthyroidism is uncommon but is more likely to occur in large breed dogs. For this reason it is advocated by some to use a dosage protocol of 0.5 mg/m2 for large breed dogs.

Therapeutic success should be judged based on clinical response and evaluation of serum T4 levels after a steady state is attained. Typically, a steady state is reached 7 to 10 days after initiating therapy. It may take weeks to months to have resolution of clinical signs referable to the initial hypothyroid state. After 6 to 8 weeks, the clinician should critically evaluate the clinical response**.** A post-pill T4 level 4 to 6 hours after oral administration of the levothyroxine provides information about the peak T4 level induced by the replacement therapy. A high normal to elevated T4 level is expected if the dog is receiving adequate supplementation. If TSH is concurrently measured, it should be normal and if previously elevated it should have decreased. A trough T4 level, just prior to the administration of the dose of levothyroxine is recommended in dogs receiving once daily administration of levothyroxine and serum T4 and fT4 by equilibrium dialysis should both be in normal range if adequately supplemented. The clinician should review a small animal internal medicine book for recommendations for concurrently managing hypothyroidism in a patient with diabetes mellitus, hypoadrenocorticism, cardiac disease or other significant concurrent illness

Conclusion

Hypothyroidism carries a good prognosis and therapy is inexpensive and relatively safe. However, many extra-thyroidal influences can change T4 values that the misdiagnosis of hypothyroidism may be as common or more common than the actual disease. The clinician should always rely on compatible clinical signs, consider the signalment as age and breed affect thyroid values and some breeds are predisposed to the development of hypothyroidism. If there is no history of drug administration that can alter thyroid levels or NTI based on history, CBC, or serum biochemistry, then diagnostic tests to

evaluate thyroid function are indicated. If results are equivocal or borderline, then retesting in 4 to 6 weeks is a reasonable approach to follow.

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## Hypercortisolism

Introduction

In 1932, an American neurosurgeon Dr. Harvey Cushing described in humans a clinical syndrome associated with a corticotroph pituitary tumor that was similar to what was described in patients with an adrenocortical tumor. Similar clinical signs, including dermatologic changes are seen in dogs and cats with hypercortisolism regardless if the hormonal disturbance results from pituitary dependent naturally occurring hyperadrenocorticism, cortisol secreting adrenal tumors or iatrogenic hyperglucocorticoidism. Many of the physiologic effects of hypercortisolism in dogs and cats are similar but each species demonstrate some unique clinical signs, and there are diagnostic testing and treatment differences.

Pathophysiology of Hyperadrenocorticism

Hyperadrenocorticism (HAC) could include the overproduction of any adrenal cortical hormone; it is most often used to refer to the overproduction of cortisol by cells in the zona fasciculata. It is important to note that cats can also have adrenal cortical tumors that secrete sex steroid hormones or intermediates that have glucocorticoid activity. Progesterone is a glucocorticoid agonist and it competes with cortisol for binding so if an adrenal tumor makes high amounts of progesterone, that can cause increased amounts of unbound cortisol. The majority of dogs and cats with HAC do in fact have true Cushing's syndrome and have a pituitary tumor that is autonomously secreting ACTH ultimately resulting in hypercortisolemia and bilateral adrenocortical hyperplasia.

In approximately 15 to 20% of dogs and cats with spontaneous HAC, the hypercortisolemia is the result of a functional adrenal tumor that autonomously secretes cortisol. Both pituitary and adrenal dependent HAC are most often due to adenomas, while a minority of animals have carcinomas with adrenal gland carcinomas being more common than pituitary carcinomas. Adrenal adenomas or functioning carcinomas cause hypercortisolemia, inhibition of pituitary ACTH production, and atrophy of non-neoplastic adrenocortical tissue.

In some instances, other hormones may also be increased. Pituitary tumors may also secrete

growth hormone, or melanocyte stimulating hormone, and some adrenal tumors can produce progesterone and other sex steroid hormones as well as cortisol.

Iatrogenic Hyperglucocorticoidism

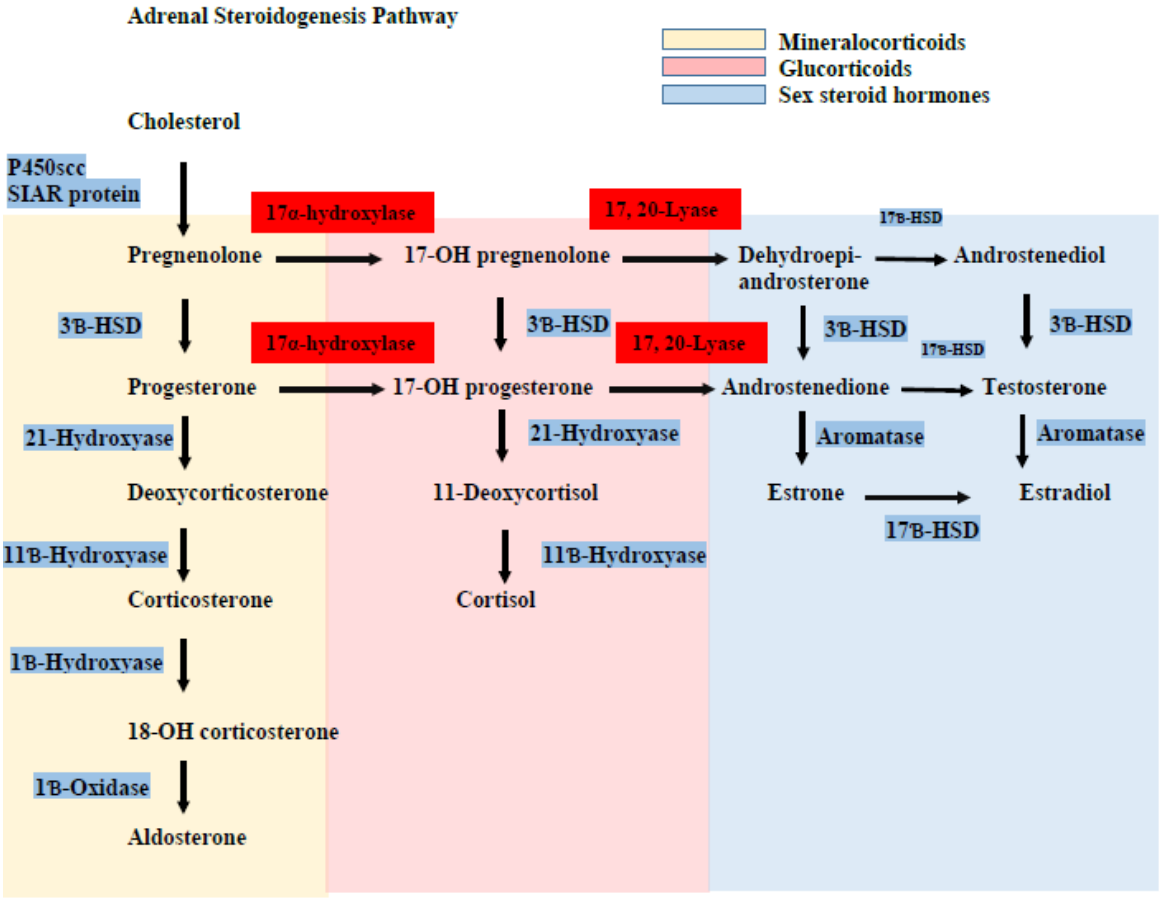
It is important to exclude any possibility of exposure to exogenous glucocorticoids before the diagnosis of Cushing's syndrome is considered. Corticosteroids are prescribed to dogs and cats for treating a variety of medical problems and their use in the management of skin disease is common. Although cats are more resistant to the effects of exogenous glucocorticoids than dogs or humans, the clinical signs in cats with chronic iatrogenic glucocorticoid administration when they occur can be similar to those seen with naturally occurring HAC. It is important for the clinician to be aware of the changes seen in dogs or cats with hypercortisolism from any cause.

Normal Pituitary-Adrenal Physiology

Cortisol regulation and production involves the hypothalamus that produces corticotropin –releasing hormone (CRH) which is delivered to the anterior pituitary via the hypothalamic- hypophyseal portal system. CRH stimulates corticotropes in the anterior pituitary gland to secrete ACTH. The hypothalamus is stimulated to secrete CRH by a number of cytokines (Il-1, IL-6 and TNF-alpha), and/or hormones (leptin, dopamine, angiotensin II, and antidiuretic hormone (ADH)). CRH release by the hypothalamus is inhibited by glucocorticoids and somatostatin but it is glucocorticoids that provide the primary negative feedback signal regulating CRH release. The pituitary regulates adrenocortical function and cortisol secretion via ACTH. The precursor molecule pro-opiomelanocortin (POMC) is cleaved into a number of biologically active fragments including ACTH, and melanocyte stimulating hormone (MSH). There are 3 functional regions of the pituitary; the anterior pituitary (composed of the pars infundibularis and pars distalis), the intermediate lobe or pars intermedia and the posterior pituitary. Different areas of the pituitary produce different hormone signals. Most important is ACTH, which in dogs has a pulsatile secretion pattern of 6 to 12 peaks in a 24 hour period. ACTH secretion is controlled by CRH, feedback inhibition from cortisol,and response to stressors (pain, acute hypoglycemia, hyopoxemia, exposure to cold, surgery and fever) that stimulate ACTH and cortisol secretions.

| | | | Product produced | Influenced by |
|---|---|---|---|---|
| Anterior pituitary | Pars distalis & Pars infundibularis | | ACTH | Stimulated by CRH, inhibit by cortisol |
| | | | Beta-LPH (physiologic role unknown) | Glucocorticoids suppress Stress & hypoglycemia increase secretion |
| Intermediate lobe | Pars intermedia | | A cells→alpha MSH & corticotropin like intermediate peptide | Involved in secretion of melanin |
| | | | B cells→POMC (cleaved to ACTH and beta-LPH | Dopaminergic inhibition |
| Posterior pituitary | Neurohypophysis | | Antidiuretic hormone Oxytocin | |

The adrenal gland has 3 layers that compose the adrenal cortex and an inner medulla. The outermost layer is the zona glomerulosa, which is the source of mineralocorticoids (aldosterone). The middle layer is the zona fasciculata, which produces cortisol, and the inner most layer the zona reticularis, which produces androgen hormones. Cytochrome P450 oxygenase enzymes mediate the synthesis of most adrenal steroids but there are differences in theses enzymes between the various adrenal cortical layers. The zona glomerulosa lacks 17-alpha-hydroxylase and is therefore unable to make cortisol or androgens. Synthesis of aldosterone is regulated by the renin-angiotensin system and serum potassium concentrations; ACTH also has a minor role. Zona fasciculata and zona reticularis layers of the adrenal cortex have 17-alpha-hydroxylase activity and are able to synthesize 17-alpha-hydroxyprogresterone and 17-alpha-hydroxypregnenolone precursors for androgens and cortisol production. ACTH, which stimulates synthesis and secretion of cortisol and androgen steroids, regulates Zona fasciculate and reticularis and chronic ACTH stimulation leads to adrenocortical hypertrophy. Absence of ACTH will result in lack of steroidogenesis and adrenocortical atrophy.




<u>Clinical Presentation Canine Hyperadrenocorticism</u>

Naturally occurring canine HAC typically affects middle aged to older dogs, and the mean age in the literature is 11 years. Majority of dogs with pituitary dependent hyperadrenocorticism (PDH) (75%) are

over 9 years of age and even higher percentage of dogs (90%) with a functional adrenal tumor (FAT) are over 9 years of age at time of diagnosis. Although there is not significant breed predisposition PDH tends to occur in smaller dogs with 75% being less than 20 kg in body weight. Almost 50% if dogs with FAT are larger than 20kg. There is a sex predilection for female dogs. Chronic hypercortisolemia causes predictable clinical signs due to metabolic and immunologic effects. Polyuria, polydipsia, polyphagia are common. Muscle catabolism, fat redistribution can result in apparent weight gain with a potbellied appearance, muscle weakness and panting. Urinary tract infections are common due to immunosuppressive effects of hypercortisolemia and because dilute urine is less bactericidal. Dogs can have neurologic signs

Clinical Presentation Feline Hyperadrenocorticism

Feline HAC is much less common that the canine disease. There is no breed or sex predilections and typically middle aged to older cats are affected, with an average age at diagnosis of between 10 to 13 years. Cats most often present as unregulated diabetics or having dermatologic disease. Concurrent diseases in cat with HAC in addition to unregulated diabetes mellitus (DM) include secondary infections of the urinary tract, respiratory tract, subcutaneous abscesses, paronychia, and bacterial cholangiohepatitis. Other concurrent diseases such as pancreatitis, chronic kidney disease (CKD), hypertrophic or restrictive cardiomyopathy and hyperthyroidism reflect diseases seen more commonly in older cats. In all species, including the cat, spontaneous HAC progresses slowly over months potentially over years before clinical signs advance sufficiently that a diagnosis is made. Polyuria and polydipsia is a common clinical sign but it may be a consequence of concurrent DM or CKD. It is not known if hypercortisolemia in cats can suppress antidiuretic hormone as occurs in dogs. Non-diabetic cats with hypercortisolism are reportedly polyphagic. When concurrent DM is present most cats will have weight loss. Muscle atrophy that occurs with hypercortisolemia is due to protein catabolism, and it can contribute to weight loss, and may cause weakness. The classically described “pot belly” that results from intra-abdominal fat distribution, hepatomegaly and loss of abdominal muscle tone is recognized to occur in cats with hypercortisolism. Cats with pituitary dependent HAC can develop neurologic signs if the pituitary tumor grows large enough.

Dermatologic Clinical Signs

Chronic hypercortisolemia can cause profound changes to the skin with suppressed proliferation of keratinocytes and fibroblasts and resultant epidermal & dermal atrophy, decreased collagen production and diminished elasticity. Follicles arrest in a haired telogen phase and clipped hair coats will as a result be slow to regrow. These physiologic changes to the skin result in symmetrical alopecia, scaling, thin skin with visible superficial vasculature, poor wound healing, increased susceptibility to bruising, Dogs with HAC or iatrogenic hypercortisolism can develop bilaterally symmetrical alopecia, thin hypotonic skin (with or without striae), increased susceptibility to bruising, easily visible dermal vasculature, phlebectasias (ventrum and medial thighs), comedones, milia, calcinosis cutis and increased susceptibility to recurrent pyoderma and adult onset demodicosis.

*Calcinosis cutis* a broad term and includes all forms of dystrophic or metastatic calcification of the skin. It is most often used for the dystrophic calcification seen in dogs secondary to hyperadrenocorticism or iatrogenic hypercortisolism. The chinchilla is the only other species to develop calcinosis cutis with hypercortisolism. In dogs, erythematous papules coalesce into firm, gritty plaques that may ulcerate and develop hemorrhagic crusts. Lesions develop in areas prone to chronic flexure movement and the dorsal cervical, axillary or inguinal areas are common lesional sites. Dystrophic calcification can also involve

mucosal membranes and the tongue. Metastatic calcification producing nodular calcium deposits in the skin, especially footpads, has been reported in dogs and cats with chronic renal failure. The author has documented calcinosis cutis lesions in the inguinal region of a dog supplemented chronically with calcitriol post-parathyroidectomy. The mineral present in calcinosis cutis has been shown by infrared spectrometry to be apatite crystals. A recent study showed predisposed breeds to include Labrador retrievers, Rottweilers, boxers and Staffordshire terriers. Lesions of calcinosis cutis typically resolve over time if the underlying metabolic disturbance can be removed. In some cases osseous metaplasia can occur. The resulting osteoma cutis lesions will not regress.

*Acquired skin fragility* in cats is associated with HAC, iatrogenic hypercortisolemia, or excessive levels of progestational compounds from either adrenal tumors or the iatrogenic effect of administered progestational compounds. Affected cats have extremely thin, fragile skin that easily bruises and can tear with simple manipulations, often during restraint or handling. Folded pinnal tips or curling of the pinnal margins can occur in cats with iatrogenic hypercortisolemia most often in association with the administration of repositol glucocorticoids. Hypercortisolism in the cat does not cause calcinosis cutis.

Clinicopathologic Abnormalities

Routine complete blood cell count and serum biochemistry panel in dogs and cats with hypercortisolism are often non-specific and can be completely normal. There are no consistent pathognomonic clinicopathologic changes in dogs or cats with HAC. Hematological findings can include a stress leukogram with leukocytosis composed of a neutrophilia, lymphopenia, and eosinopenia in both dogs and cats and some cats may have a mild anemia present while dogs may have a mild erythrocytosis and thrombocytosis. Elevated liver enzymes (alkaline phosphatase (ALP) and alanine transferase (ALT)) are often in increased in the dog. Liver enzyme elevations can occur in the cat but since the cat does not have a steroid induced isoenzyme of ALP, any increases in this enzyme is likely associated with concurrent diabetes mellitus, pancreatitis or some primary hepatic disease. Eighty percent of affected cats have hyperglycemia due to overt diabetes mellitus, transient diabetes or stress hyperglycemia. Mild hyperglycemia unassociated with diabetes can be seen in dogs with HAC. In dogs with HAC hypercholesterolemia and hypertriglyceridiemia (if measured) can be documented. Urine specific gravity is typically below 1.020 in the dog, but usually well above 1.020 in the cat, even if the cat has polyuria. The majority of dogs and cats with hypercortisolism have some degree of proteinuria.

Endocrine Tests for HAC

*Urine Cortisol: Creatinine Ratio (UCCR)*. The UCCR is a good screening test for HAC in the dog and cat but when interpreting results it is important to remember that the cat has higher UCCR values than dogs and their own reference range. Cortisol can increase with stress and other illnesses so two morning urine samples should be collected at home which may present challenges for some cat owners. For feline patients this is easiest if owners use a nonabsorbent cat litter. The UCCR has excellent sensitivity and a normal value rules out the possibility of HAC. As the test has a low specificity, a positive result needs to correlate to history and clinical signs and then the diagnosis needs to be confirmed with further diagnostic testing.

In the dog and the cat, the UCCR can be combined with an oral high dose dexamethasone suppression test (HDDST) to differentiate between adrenal versus pituitary dependent hyperadrenocorticism. This combined test is done in the cat, as the HDDST alone does not reliably differentiate between the two forms of HAC in the cat. If the last UCCR measurement after administration of three oral doses of dexamethasone is <50% of the mean of the baseline UCCR values

than the result is consistent with pituitary dependent HAC (PDH). If the initial two UCCR values are within reference range than HAC is ruled out, so this combined test can be both a screening and a discriminatory test.

*Hair Cortisol*
Two studies have reported that hair shaft cortisol concentrations are higher in dogs with HAC compared to normal control dogs. Further studies are needed to determine its efficacy as a reliable screening test.

*Low Dose Dexamethasone Suppression Test (LDDST).* Dexamethasone suppression tests are used to evaluate the appropriateness of the physiologic feedback of the pituitary gland when an exogenous dose of a glucocorticoid is administered to the animal. The LDDST is the preferred screening test for evaluating both dogs and cats with suspected HAC as it has high sensitivity ( 90-95% of PDH dogs and 100% of AT dogs) and moderate specificity (50%) as non-adrenal illness, especially if chronic can influence the LDDST. Healthy cats require a higher dose of dexamethasone to achieve consistent suppression than what is needed in dogs. Consequently, the dose for a LDDST in cats is tenfold higher at 0.1 mg/kg. This test does not identify iatrogenic hypercortisolemia

Lack of suppression of cortisol at either 4 hours and/or 8 hours confirms inappropriate functioning of the pituitary adrenal axis and supports the diagnosis of HAC. Suppression at 4 hrs (≤ 40 nmol/L (1.4 μg/dL)) with escape at 8 hrs is seen in approximately 30% of dogs with PDH. Dogs with a cortisol concentration at either 4 or 8 hrs that suppresses to <50% of baseline (pre dexamethasone) are most likely to have PSH. In about half of cats diagnosed with HAC with a LDDST the values obtained can be used to discriminate between PDH and adrenal dependent HAC (ADH). If the 4-hour cortisol value is ≤ 40 nmol/L (1.4 μg/dL) or the 4-hour or 8-hour cortisol value is > 40 nmol/L (1.4 μg/dL) but is < 50% of the baseline 0 hour value then PDH is diagnosed.

*ACTH Stimulation Test.*
The ACTH stimulations test evaluates adrenal cortex reserve and is the test of choice for identifying iatrogenic hyperglucocorticoidism, which causes adrenocortical atrophy and failure to respond to ACTH stimulation. Dogs with naturally occurring HAC may have a normal or exaggerated response to exogenous ACTH. The sensitivity of ACTH stimulation test in dogs is 85% for the diagnosis of PDH and 60% for the diagnosis of FAT, while the specificity is 85% to 90%. This test has poor sensitivity as a screening test for spontaneous HAC in the cat. It has only moderate specificity and cats with other non-adrenal illness can have post- ACTH stim values outside the reference range. It is also the test used to monitor therapy when trilostane or mitotane is utilized for medical management.

*High Dose Dexamethasone Suppression Test (HDDST).*
This is a test used to differentiate PDH from FAT in the dog, since a higher dose of dexamethasone will override resistance to suppression seen with some PDH dog on a LDDST while if a dog has a FAT no dose of dexamethasone will suppress cortisol levels. Dogs with large pituitary tumors are less likely to suppress even with a higher dose of dexamethasone. Consequently, lack of suppression on the HDDST does not always differentiate between PDH and FAT and if dexamethasone resistance is identified on a LDDST other differentiating tests such as abdominal ultrasound or measuring endogenous ACTH. For this test in the cat, a higher dose than in the dog, of 1mg/kg is given IV and serum cortisol values are measured pre-administration, and at 4- and 8-hour post-administration. Only 40 to 50% of PDH cats will show > 50% suppression of baseline cortisol at 4 or 8 hours, consequently it is no longer recommended as a discriminatory test.

*Endogenous ACTH and ACTH Precursors.* Measuring endogenous ACTH can be used as a discriminatory test. Dogs and cats with PDH are expected to have normal or increased endogenous ACTH plasma levels, while animals with ADH will have decreased levels. About 20% of HAC dogs will have eACTH within a non-diagnostic range so other differentiating tests will be needed. Some normal cats will have ACTH levels below reference range so this is not used as a screening test for HAC. Samples need specific handling; placed in EDTA tubes and kept on ice and spun in a cold centrifuge to separate the plasma and shipped to the lab on dry ice. Improperly handled samples cause falsely low measurements which would incorrectly support diagnosis of ADH. Endogenous ACTH precursors (pro-opiomelanocortin (POMC) and pro-ACTH) were reported to be higher in cats with HAC than cats with acromegaly and DM or cats with only DM alone. However, this is not a commercially available test.

Diagnostic Imaging

Diagnostic imaging can provide valuable information to confirm the diagnosis of naturally occurring HAC and to differentiate between pituitary and adrenal dependent HAC. It can also aid in making treatment decisions,

*Abdominal Ultrasonography.* Adrenal glands can be evaluated by abdominal ultrasound however, it is important to remember that their size can also be influenced by non-adrenal disease, such as hyperthyroidism in the cat, which can increase adrenal glands by as much as 20%. The experience of the ultrasonographer will also influence the sensitivity of this imaging technique as a discriminatory test. Dogs and cats with PDH have bilateral symmetric enlargement of the adrenal glands while animals with ADH have a visible adrenal mass with typically atrophy of the other adrenal gland. In animals with adrenal tumors, the presence of invasion into nearby vascular structures or evidence of metastatic spread should also be assessed. Occasionally both dogs and cats can have bilateral adrenal tumors with different functional cell types. The abdominal ultrasound can also evaluate for evidence of pathology in other organs and provide more information about any concurrent diseases.

*Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).* Performing advanced imaging of the pituitary gland is necessary to determine the size of the corticotrope tumor. This is an important diagnostic test to consider, as macroadenomas are present in approximately 50% of cats with PDH and 50% of dogs have a visible pituitary tumor on imaging. Confirming the presence of a macroadenoma provides relevant information to guide therapeutic choices since medical treatment does not slow the progression of a macro-adenoma and any associated neurologic signs. Advanced imaging of the abdomen can provide more information about adrenal tumor size and degree of tumor invasion particularly nearby vascular invasion that is helpful in surgical staging. It is reasonable to consider performing both imaging studies under one general anesthesia to determine best therapeutic options.

Medical Treatment of Hyperadrenocorticism

*Trilostane.* Trilostane is a synthetic steroid analogue that competitively inhibits 3-β-hydroxysteroid dehydrogenase which is the enzyme needed to convert pregnenolone and 17-α-hydroxypregnolone to progesterone and 17–α-hydroxyprogesterone, precursors in cortisol synthesis. Trilostane is well tolerated by most dogs and side effects if they occur are typically mild resulting from low cortisol and /or aldosterone. Severe adverse effects can occur including marked GI signs, and acute adrenal necrosis. Overdose of trilostane may cause adrenal suppression that persists for days to months if adrenal necrosis has occurred. Increasing endogenous ACTH may be associated with adrenal necrosis so careful monitoring to avoid hypocortisolemia may decrease risk of adrenal necrosis. Trilostane is initially

administered as an oral dose of 0.5 to 1.0 mg/kg every 12 hours. If any worrisome side effects develop, the drug should be discontinued and the dog evaluated with blood glucose, electrolytes, renal parameters and ACTH stimulation test to assess dose.

The pharmacokinetics of this drug in cats is not known and recommendations about using it in cats is extrapolated from dogs. The drug is given at 1 to 2 mg/kg orally twice a day. Side effects of trilostane in cats, as in dogs, include vomiting, diarrhea and hyporexia and may be due to the drug or result of inducing hypocortisolemia.

Monitoring response to therapy includes assessment of the dog or cat's activity, appetite and water intake and urination habits and results of an ACTH stimulation test performed 2 to 4 hours after feeding and administration of trilostane. Consistency of when the ACTH stim test is done is important during monitoring. Dermatologic lesions can be monitored for improvement but care should be taken when restraining HAC cats.

The extent of adrenal suppression is assessed by the ACTH test and the dose of trilostane is then adjusted. The ACTH stimulation test can be combined with a UCCR test to determine if dose or administration frequency need to be adjusted. The majority of dogs are managed with trilostane and majority of cats attain some favorable clinical response with trilostane although complete resolution of all clinical signs is rare.

*Lysodren (Mitotane).* Mitotane is an adrenocortolytic drug that is cytotoxic to the zona fasciculata and reticularis layers of the adrenal cortex. The zona glomerulosa is less sensitive to the cytotoxic effects of the drug but at higher doses, mitotane can cause complete necrosis of the adrenal cortex. The drug is fat-soluble and needs to be administered with a meal. The standard protocol attempts to preserve the function of the zona glomerulosa and selectively damage the cortisol producing layers. There is also a nonselective protocol with a goal to cause complete necrosis of the adrenal cortex and will require management for hypoadrenocorticism. Mitotane is less effective than trilostane in the cat and is not recommended as a first line therapy as it does not often control clinical signs.

Side effects of the drug in both dogs and cats include vomiting and hyporexia these can be signs seen from the drug itself or if hypoadrenocorticism develops.

*Other Medical Therapies.*

In some parts of the world, trilostane and mitotane may not be available or occasionally a do may not tolerate either drug. A number of other drugs (aminoglutethimide, bromocriptine, cyproheptadine and metyrapone) have been evaluated for treating canine HAC with limited favorable response. Ketoconazole can inhibit steroidogenesis if administered at doses higher than prescribed for treating fungal disease (20 mg/kg/day) and can directly suppress ACTH. Selegiline hydrochloride is an irreversible inhibitor of monamine oxidase which will increase dopamine and may down regulate ACTH secretion from pars intermedia (30% of dogs with PDH have a pars intermedia tumor. Adrenocortical function testing have shown that this drug is ineffective although owners may report clinical improvement likely because the drug is metabolized into amphetamine like substances which could account for increased activity and alertness of dogs receiving this medication. Cabergoline is a D2 dopaminergic receptor agonist with a high affinity for the pituitary that has anti-proliferative, pro apoptotic and affecting cleavage of ACTH to yield alpha MSH. It is most effective in dogs with pars intermedia tumors with 40 to 60% of dogs having some favorable response. Adverse GI signs and hair coat changes occur in about 10% of dogs. Retinoic acid suppresses tumor synthesis of POMC and ACTH and suppresses tumor growth (owners need to be warned of the human teratogenicity risk

associated with the drug). Cabergoline and retinoic acid together are synergistic in particular in dogs with pars distalis and pars intermedia tumors.

The use of other steroid hormone synthesis inhibitors such as metyrapone, ketoconazole, and aminoglutethimide have been reported in small numbers of cats with HAC with limited efficacy or development of adverse effects and consequently they are not currently recommended therapies for feline HAC.

Surgical Treatment of Hyperadrenocorticism

*Adrenalectomy.* Unilateral adrenalectomy for ADH or bilateral adrenalectomy for PDH are associated with high risk of post-operative complications. Mortality often occurs in the first post-operative week. Bilateral adrenalectomy will require lifelong hormone replacement therapy with both glucocorticoids and mineralocorticoids and it will not alter progression of a macroadenoma. In cats, one-year survival rates after adrenalectomy have been obtained in 50 to 70% of reported cases.

*Hypophysectomy.* A transsphenoidal hypophysectomy for PDH in theory can be curative. The 1-year survival rate after hypophysectomy in dogs was 86%, and the 4-year survival rate was 79% (which is comparable to trilostane or mitotane therapy). It has only been described in the literature in 9 cats with PDH and only 3 cats survived for more than 15 months, Post-operative hormone replacement therapy with cortisone acetate, levothyroxine and desmopressin will be required. This is not a widely available surgical option.

Radiation Therapy for PDH

Radiation therapy is recommended for dogs and cats with PDH that have macroadenomas causing neurologic side effects. Concurrent trilostane therapy can also be implemented. Improvement in neurologic signs may take weeks to months and signs associated with hypercortisolemia can also improve. Clinical response in dogs is dependent on size of tumor, dogs with larger pituitary tumors do not do as well. Survival times of 1 to 2 years have been reported in the cat.

Treatment of Iatrogenic Hyperglucocorticoidism

When prescribing glucocorticoids for the management of any disease it is important to be in contact with the pet owner and to reassess the dog or cat for both desired clinical response but also the development of significant side effects from corticosteroid administration. If these develop, then alternative drug options should be considered and glucocorticoids slowly tapered. The longer the glucocorticoid therapy has been administered the more slowly the tapering protocol should be.

Prognosis

*Canine Cushing's disease*: most dogs have a good or excellent response to treatment. Dogs that are symptomatic for a macroadenoma, have concurrent hypertension or diabetes mellitus may have a worse prognosis.

*Feline Cushing's syndrome* has a poor prognosis and it is often not diagnosed until the disease is advanced. As it occurs in older cats, there are often concurrent disease(s) present and owners may elect not to pursue any therapy for the HAC. Surgical options for treatment are most effective but have relatively high morbidity and mortality associated with them, as these cats are not good surgical candidates. The goal of medical therapy with trilostane is to control clinical signs and facilitate management of the concurrent DM. Untreated, most cats are euthanized within a month of diagnosis.

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**Sex Steroid Hormone Disturbances**

Estrogen: Hyperestrogenism

Increased estrogen can arise from cystic ovaries, granulosa cell tumors, testicular tumors (Sertoli cell tumors most commonly) or iatrogenically from estrogen supplementation for urinary incontinence or second hand exposure to human topical estrogen products used for hormone replacement therapy. Estrogen inhibits anagen initiation resulting clinically in alopecia. Hyperpigmentation is often present and can be diffuse or macular. Alopecia often begins in the perineal, caudal thigh, inguinal and flank regions. A distinctive line of erythema or hyperpigmentation along the midline of the prepuce is a characteristic cutaneous lesion. Identification and correction of the underlying cause of hyperestrogenism may require abdominal ultrasound of ovarian tissue or cryptorchid testes or ultrasound of the testicles. If gonadal pathology is identified ovariohysterectomy or castration is indicated. In the already spayed female or neutered male possible exposure to exogenous sources of estrogen

(diethylstilbestrol) for urinary incontinence or exposure to human use of estrogen topical therapy needs to be evaluated.

Progesterone

Progesterone is a glucocorticoid agonist and it competes with cortisol for binding so if an adrenal tumor makes high amounts of progesterone that can cause increased amounts of unbound cortisol. Cats can develop acquired skin fragility dues to increased progesterone synthesis or iatrogenic effect of administered progestational compounds.