Canine hypothyroidism, while a common endocrinopathy in the dog, may be over diagnosed due to confusion/inconsistencies in establishing a definitive diagnosis.

**Etiology/pathophysiology**
Hypothyroidism is due to decreased thyroidal production of the thyroid hormones thyroxine (T4) and triiodothyronine (T3). Greater than 90% of cases are primary and are due to acquired immune mediated destruction of the thyroid gland which is preceded by thyroiditis, idiopathic atrophy or less commonly neoplasia. Secondary forms of the disease include thyroid stimulating hormone (TSH) deficiency, pituitary neoplasia, and cystic Rathke’s pouch, are uncommon clinical entities. Tertiary hypothyroidism with thyrotropin releasing hormone (TRH) deficiency has not been documented in dogs. Congenital cases have been reported in both dogs and cats.

**Signalment/history**
Hypothyroidism most commonly occurs in young to middle aged dogs with an average age of 7 years. Dogs with autoimmune disease tend to develop hypothyroidism at a younger age. While thyroid values decrease within the reference range in senior dogs, hypothyroidism is very uncommon and other factors (see below) are likely responsible for the observed decreased thyroid concentrations in euthyroid older patients. Spayed females and neutered males are at an increased risk when compared to sexually intact animals. Breed predispositions have been reported for golden retrievers and Doberman pinschers. Thyroiditis is heritable in the beagle, Borzoi, golden retriever, great Dane, Irish setter, Doberman pinscher, and old English sheepdogs.

**Risk factors**
No known environmental factors have been identified. Breed predispositions as outlined above.

**Historical findings**
As thyroid hormone regulates the metabolic rate and influences the functions of many organs, clinical signs are often non-specific and insidious in onset. Many other diseases can have similar clinical signs to hypothyroidism, which may lead to an incorrect diagnosis. As such laboratory testing of thyroid function is often performed as part of the diagnostic work in animals with non-thyroidal illness.

**Clinical features**
Common clinical signs include lethargy, mental dullness, weight gain, exercise intolerance, alopecia, and obesity.

**Differential diagnosis**
Many metabolic, infectious, neoplastic, congenital, degenerative, and inflammatory diseases can cause similar clinical signs and biochemical abnormalities seen with hypothyroidism.

**Diagnostics**

**Laboratory diagnosis**
Thyroxine is the major secretory product of the thyroid while the majority of T3 is derived from extra-thyroidal sources. Both T4 and T3 are highly protein bound to serum carrier proteins such as thyroid binding globulin, transthyretin and albumin. Only unbound (free) hormone is able to penetrate cell membranes, bind to receptors and result in biologic activity. Protein bound hormone acts as a reservoir to maintain steady concentrations of free hormone in the plasma despite rapid alterations in release and metabolism of T3 and T4 and changes in the plasma protein concentrations.

**Serum total T4**
Serum T4 is a sensitive (>90-95%), but not specific test (70-75%) 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 diagnosis of hypothyroidism can be ruled out if the T4 is in the upper 50% 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. In house testing of TT4 is not recommended.

**Serum total T3**
Serum T3 concentration is an unreliable test for evaluation of thyroid function.

**Serum free T4 (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 (sensitivity > 95%, specificity > 97%). 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 non-thyroidal factors that can influence
total T4 are present. Free T4 is less affected by most non-thyroidal 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 non-thyroidal illness is present, and if autoantibodies to T4 are detected.

**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, as such it lacks sensitivity for use as a screening test. The combination of decreased total T4 or fT4 with an elevated serum TSH is diagnostic of hypothyroidism (specificity > 95%). Therefore, a normal TSH does not rule out hypothyroidism, but an elevated TSH combined with a low T4 or fT4 provides a definitive diagnosis.

**Diagnosis of thyroiditis**

Antibodies against either T4 or T3 or both are sometimes present in dogs with thyroiditis with or without hypothyroidism. The presence of these antibodies does not indicate that the dog is hypothyroid, but suggests that autoimmune thyroid disease is present. These antibodies frequently cause false elevation of T4 or T3 concentrations that can result in marked elevation of the hormones. Autoantibodies to T4 are present in about 10-15% of hypothyroid dogs.

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. In one long-term study at Michigan State University, 20% of asymptomatic, antithyroglobulin positive dogs with normal thyroid function progressed to hypothyroidism in 1 year. The presence of these antibodies in a dog with borderline laboratory evidence of hypothyroidism and clinical signs supports a diagnosis of hypothyroidism.

**Additional considerations**

**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, Saluki’s and whippets also have total T4 concentrations that are well below the mean concentration of dogs in general. 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.

**Time of day**

In one study 50% of normal dogs had a low serum T4 concentration at some time during the day.

**Medications**

The drugs that are known to commonly alter thyroid function tests are glucocorticoids, phenobarbital, sulfonamides, clomipramine, aspirin, and some other NSAIDs. 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. The changes may be 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.

**Nonthyroidal illness**

Illness not involving the thyroid gland can alter thyroid function tests and has been labeled "non-thyroidal 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 non-thyroidal illness. Serum fT4 measured by equilibrium dialysis is less likely to be affected, but can also be increased or decreased. However, in dogs with substantial non-thyroidal illness, the fT4 is likely to be decreased. It is recommended that testing of thyroid function be postponed until the non-thyroidal illness is resolved. If this is not possible, measurement of T4, TSH and fT4 are indicated.

**Ancillary testing**

**Thyroid gland ultrasound**

Although rarely necessary, ultrasound of the thyroid glands (by an experienced ultrasonographer) can be used to aid in differentiating dogs with primary hypothyroidism from those with non-thyroidal illness. Thyroid glands of hypothyroid dogs tend to be smaller, less homogeneous, and hypechoic than those of euthyroid dogs. There is considerable overlap with the ultrasonographic appearance and size of the thyroid glands of euthyroid and hypothyroid dogs. Thyroid ultrasound can only be used to help support a diagnosis of hypothyroidism if the thyroid glands are quite small.
Therapeutics

Drugs

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, in clinical practice some dogs seem to respond better to twice-daily treatment.

The initial starting dose is 0.02 mg/kg PO q 24 h. In general you will never have to exceed 0.8 mg as an initial daily dosage even in very large dogs. If the dog has significant cardiovascular disease, diabetes mellitus, or hypoadrenocorticism, treatment should be instituted at 25% of the standard dose, with the dosage increased by 25% every 2 weeks based on clinical response and post-pill testing. Most dogs show improvement within the first 1-2 weeks, with increased activity, improved attitude, and partial or complete resolution of neurologic signs. The cutaneous manifestations of hypothyroidism may take several weeks to months to resolve. Post treatment monitoring may be carried out but clinical response is the most important monitoring tool. Peak T4 concentrations generally occur 4-6 hours after administration of levothyroxine and should be in the high normal to slightly above normal range (40-70 nmol/L). However, the bioavailability of thyroxine ranges from 13 to 87% in the same dog from day to day bringing into the question the utility of random post pill monitoring of TT4. It is likely more meaningful (though more expensive) to measure TSH (especially if the TSH concentration was elevated pre-treatment) or fT4 concentrations after replacement therapy has been started, especially in animals that show a poor clinical response to therapy. Serum TSH concentrations should be in the normal range or undetectable and fT4 concentrations should be in the normal range. Serum concentrations of TSH and fT4 should not be performed until the patient has been on supplementation for at least 2 weeks. If the patient was initially started on twice daily therapy, treatment can be reduced to once daily treatment when a good clinical response has been obtained.

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.

Comments

Expected course and prognosis

Response to therapy should be observed in the first 4-8 weeks post treatment. Improvements in mentation and physical activity may be noted within the first week though some abnormalities, especially dermatologic signs, may take several months to resolve. An absent or incomplete response to therapy may be due to an incorrect diagnosis, poor owner compliance, inadequate dosing, or poor absorption.
How I Treat Diabetes in Cats
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Diabetes mellitus is a common endocrine disorder in dogs and cats. Recent data has shed light on the pathogenesis of the disorder in dogs and cats and has highlighted the role of diet, insulin and novel hypoglycemic therapies. In the majority of cases, the most appropriate therapy in both dog and cats includes the administration of insulin.

The key to successful management of the diabetic patient lies in close communication with the pet owner and prompt recognition and treatment of concurrent disorders.

Key facts
1. Insulin is still the mainstay of therapy in the majority of dogs and cats with diabetes mellitus.
2. Diet is an important part of diabetic management especially in obese patients and cats.
3. Auto-immune disease, pancreatitis and amyloidosis are the most common causes of diabetes in dogs and cats.

Successful management of the diabetic patient involves many factors. An understanding of dietary therapy, insulin preparations, oral and novel hypoglycemic agents and management of concurrent illness, are all required to optimize glycemic control. The goals of therapy are to control clinical signs, prevent or slow the progression of cataracts, avoid hypoglycemia and maintain ideal body weight. An additional goal in cats is to obtain remission. The challenge is to address these concerns while attempting to help the owners deal with what they may consider a time consuming, expensive and chronic medical condition.

Diabetes Mellitus in dogs and cats results from a decrease in insulin secretion from the beta cells of the pancreas and/or a decrease in insulin action. There are three classifications of diabetes:

Type I diabetes is comparable to insulin dependent diabetes mellitus (IDDM) in humans. It results in low basal insulin concentrations with impaired insulin secretion following a glucose load. Treatment requires insulin injections. It is the most common form of diabetes in dogs.

Type II diabetes is similar to non-insulin dependent diabetes (NIDDM) in humans and is managed with dietary therapy and oral hypoglycemics. It causes normal to increased basal insulin concentrations with decreased secretion following a glucose load. Insulin may or may not be required for animals with Type II diabetes.

Type III diabetes is seen most commonly in hormonally-induced diabetes in dogs and cats and is similar to impaired glucose tolerance (IGT) in humans. Diabetogenic hormones (epinephrine, cortisol, glucagon and growth hormone) or medications interfere with insulin action and cause glucose intolerance, which can lead to diabetes.

Etiology and signalment
Feline
The most common causes of diabetes in cats are obesity, pancreatitis and most commonly, amyloidosis of the pancreatic beta cells. There appears to be very little gender predisposition to this disease in cats, although it is slightly more common in males than females. As with dogs, the onset of diabetes in cats occurs most often in middle age.

Clinical signs
The clinical signs of diabetes include PU/PD (polyuria and polydipsia) from hyperglycemia, resulting in glycosuria and a resultant osmotic diuresis. Polyphagia and weight loss is common although many animals will still be obese upon presentation. In addition to the polyphagia, there may be variable degrees of dehydration especially in the cat. Cataract formation is very common in dogs with diabetes, but rare in cats. Cats often present with icterus as a result of concurrent hepatic lipidosis and/or pancreatitis. Icterus is not common in dogs unless they have pancreatitis. Cats may also exhibit a plantigrade stance (peripheral neuropathy) that is directly related to the severity and duration of hyperglycemia. Clinical neuropathies do occur in dogs, but are extremely rare.

Differential diagnoses include: hyperthyroidism (in cats), gastrointestinal lymphoma, hepatic disease, renal disease, pancreatitis, hyperadrenocorticism, and acromegaly.

Diagnosis
Diagnosis involves testing for persistent fasting hyperglycemia, with fasting blood glucose greater than 200mg/dl. Clinicians also will need to rule out transient hyperglycemia that may be due to: post-prandial hyperglycemia; diabetogenic hormones (endogenous or exogenous); and stress hyperglycemia. Stress hyperglycemia can be a problem in cats due to the release of epinephrine when stressed or handled.
Laboratory abnormalities include:

- Hemogram
  - non-specific
  - signs of dehydration

- Biochemistry profile
  - hyperglycemia
  - increases in SAP and ALT
  - increases in bilirubin (usually in cats)
    - hepatic lipoidosis
    - pancreatitis

- Urinalysis
  - glycosuria
    - renal threshold for glucose
      - canine 180-220mg/dl
      - feline 240-300 mg/dl
  - ketonuria
  - up to 40% of patients will have positive urine cultures in the absence of an active urine sediment.

Treatment

The number one cause of death in diabetic dogs and cats is not the disease itself, rather, it is the owner's frustration with the disease. This is an extremely important point to remember when treating diabetic animals. Good communication with the pet owner is perhaps the most important component of managing the disease.

It is recommended that clinicians schedule a 30-minute appointment with the client at the time of discharge before sending the diabetic patient home for the first time. During this appointment, clinicians should thoroughly discuss the care required for the patient. Include the following instructions in that discussion: how to give the animal injections; how to store insulin, what types of food to feed and how often; how to recognize the signs of hypoglycemia and how to react to this condition. Also include information on what clinical signs to look for in terms of monitoring water intake and urine production. The client should be given written instructions for use as a reference once they are caring for the patient at home. It is essential that the clinician and veterinary staff strive to educate the caregiver and motivate them to get involved in the care of their diabetic pet.

The goals of treatment include elimination of the clinical signs of diabetes, prevention or slowing of cataract formation and resulting blindness, prevention of potentially dangerous hypoglycemia, and prevention and/or treatment of concurrent illness.

Therapy for diabetes centers on three main areas: Treatment of concurrent illness (i.e., urinary tract infections, pyoderma, etc.), insulin therapy, and dietary management.

Concurrent illness

Monitoring for concurrent illness is very important in effectively managing diabetic dogs and cats. Clinicians must effectively recognize and treat the other disorders because the concurrent illness will impact the diabetic regulation and many common diseases have similar clinical signs to diabetes mellitus. Even simple problems such as UTI's and pyoderma can result in activation of stress hormones and result in insulin resistance.

Insulin therapy

There has been a considerable amount of confusion over the various insulin preparations that are available. In general, animal origin insulins are being discontinued as the desire and ability to treat people with human derived insulin preparations has progressed.

There is concern that animals receiving human insulin will develop antibodies resulting in decreased insulin activity and/or effectiveness. Dogs receiving any insulin product that is not derived from pork may make antibodies. However, studies have shown that those antibodies do not interfere with the glucose control. In fact, dogs that made antibodies against insulin had a longer duration of insulin action, which actually enhanced the effect of the insulin rather than decreased its efficacy. A recent study in cats should that 13% developed anti-insulin antibodies. None of the cats should signs of insulin resistance.

The options with human insulin include ultra short acting, short acting, intermediate acting, and long-acting insulins. The short acting insulins are primarily used for ketoacidosis, and therefore, are not covered in this article. The intermediate acting insulins are classified as either NPH or Lente. It is important to note however, that even though they are classified as intermediate, they do not behave the same way in the dog or cat. Lente is actually a mixture of two different insulin preparations, which results in a bimodal onset of actions. This is helpful in some patients because it helps block post-prandial hyperglycemia. Conversely, a lente insulin is not recommended for use in an animal that does not develop post prandial hyperglycemia. It is recommended that NPH be used in the
majority of dogs and cats with diabetes and it is also understood that most patients will require two injections a day to achieve glycemic control.

**Feline patients**

**Newly diagnosed patients**

1. Insulin glargine (Lantus): Glargine is a modified, recombinant, long acting insulin analog. A study presented at ACVIM in 2005 showed a very high rate of remission (8/8 in remission within 4 months with 6/7 still in remission at 1 year) in feline diabetics with the use of glargine and a low carbohydrate-high protein diet. The recommended starting dose is 0.5 units/kg BID if the fasting blood sugar is greater than 360 mg/dl and 0.25 units/kg BID if the initial fasting blood glucose is less than 360 mg/dl. For additional product information see: www.lantus.com. Glargine highlights:
   a. Should not be diluted or mixed as this will affect pH
   b. Should be kept refrigerated. Once open the vial has a shelf life of 4 weeks at room temperature. I would discard any remaining insulin after 8 weeks of refrigeration pending further clinical data.

2. PZI: As with dogs we only recommend the use of PZIR from BI.

3. Humulin N and Novolin N: Similar to PZI with remission rates of 40-50 % when used with a low carbohydrate-high protein diet. Starting doses are generally 1-3 units/cat once a day.

4. Vetsulin: Again similar to PZI and Humulin N with remission rates of 40-50 % when used with a low carbohydrate-high protein diet. Starting doses are generally 1-3 units/cat once a day.

**Transitioning feline patients**

If you have patients currently taking either Humulin L or Humulin U, I would switch them to either Vetsulin or Humulin N. The initial starting dose will remain the same with re-assessment of clinical signs and a serial blood glucose curve performed 1 week after changing insulin preparations. If you wish to transition them to glargine, I would follow the dosage recommendations as outlined above under newly diagnosed patients. It is important to note that remission rates will be much lower with glargine and a low carbohydrate-high protein diet in long standing diabetic patients (cats with diabetes for more than 6 months) than in newly diagnosed patients.

With the recent introduction of the AlphaTrak Blood Glucose Monitoring System (Abbott) we have the ability to very accurately measure blood glucose concentrations in both dogs and cats using very small quantities of blood. This will allow both veterinarians and pet owners to obtain very reliable results in both the hospital and home setting. This information can then be used to make informed decisions regarding the management of diabetic patients. These decisions impact the type and dose of insulin selected, the frequency of insulin administration, aid in the assessment of glycemic control, help in preventing hypoglycemic episodes and monitor for remission of diabetes especially in feline patients.

Glycemic control can be evaluated in a numbers of ways. Owner assessment of clinical signs (polyuria, polydipsia, weight gain or loss), progression of diabetic cataracts (dogs), presence of peripheral neuropathy (cats), and episodes of hypoglycemia are often the best indicators of glycemic control. Changes in insulin dosage or documenting remission of diabetes, is best determined by blood glucose measurement. Recognizing that the measurement of blood glucose concentrations can be problematic in the hospital setting (especially in cats as a result of stress induced hyperglycemia) recent work has evaluated the practicality and value of at home blood glucose monitoring in dogs and cats. At home blood glucose monitoring is essential in the management of human patients with diabetes given that a number of the complications associated with long term diabetes are directly related to persistent hyperglycemia. While diabetic retinopathy, nephropathy, painful neuropathies and cardiovascular disease are rare in our veterinary patients, adequate glycemic control is required to eliminate clinical signs and decrease morbidity and mortality in dogs and cats. Control of clinical signs does not require the restoration of euglycemia but rather involves keeping the blood glucose levels below renal threshold for the majority of the day. Renal threshold for glucose is 180 mg/dl in the dog and approximately 280 mg/dl in the cat. It is very important that we remember the owners of diabetic dogs and cats are being asked to do a great deal to help in the management of their pet’s chronic illness and we need to do whatever we can to make the clients job easier while at the same time taking steps to assure maximal diabetic control.

**Using the information derived using at home or in hospital glucose monitoring**

The data obtained with at home blood glucose monitoring in conjunction with clinical signs is used to adjust the dose of insulin and to monitor for remission of diabetes. We will look at scenarios for both cats and dogs. The recommendations for cats are based on our experience as well as the data generated by Dr Jacquie Rand at the University of Queensland.

**Cats**

1. Cats on Glargine and PZI Insulins
   a. If the preinsulin blood glucose concentration is > 360 mg/dl and/or the nadir blood glucose (PZI) or 4 hour (glargine) post blood glucose concentration is > 180 mg/dl the dose of insulin is increased by 0.5 to 1 unit BID.
b. If the preinsulin blood glucose concentration is 270 to 360 mg/dl and/or the nadir glucose (PZI) or 4 hour (glargine) post blood glucose blood glucose concentration is 90 - 180 mg/dl the dose of insulin is maintained.

c. If the preinsulin blood glucose concentration is 190 - 270 mg/dl and/or the nadir glucose (PZI) or 4 hour (glargine) post blood glucose blood glucose concentration is 54 - 90 mg/dl use the nadir, clinical signs and the next preinsulin glucose concentration to determine if the dose is decreased or maintained.

d. If the preinsulin blood glucose concentration is < 180 mg/dl and/or the nadir blood glucose (PZI) or 4 hour (glargine) post blood glucose blood glucose concentration is < 54 mg/dl the dose of insulin is decreased by 0.5 to 1 unit BID. If the total insulin dose is already 0.5 – 1 unit BID, stop the insulin and check for diabetic remission.

2. Cats on NPH, Lente or Ultralente Insulins

   a. If preinsulin blood glucose is < 210 mg/dl withhold insulin and check for diabetic remission.
   b. If preinsulin blood glucose is 234 - 288 mg/dl total insulin dose should not be higher than 1 unit BID.
   c. If nadir blood glucose is < 54 mg/dl insulin dose should be reduced by 50%.
   d. If nadir blood glucose is 54 - 90 mg/dl dose should be reduced by 1 unit BID.
   e. If nadir blood glucose is 91 - 162 mg/dl insulin dose should remain the same.
   f. If nadir blood glucose is > 180 mg/dl insulin dose should be increased by 1 unit BID.

**Diet**

There is a considerable amount of reliable research data showing that diets high in carbohydrates, low in fat and high in fiber are helpful in regulating diabetic dogs. These types of diets lower the average insulin dose, the average blood sugar, the amount of urine being produced and glycosolated hemoglobins and fructosamine levels.

The carbohydrates in these diets are complex carbohydrates. It is important to avoid diets high in simple sugars, which includes any commercial semi-moist food, primarily those packaged in foil packets. Diets high in simple sugars are absorbed very rapidly before the insulin has time to work. The goal with diet is to balance the absorption of sugar with the onset of action of the insulin. A high carbohydrate/low fat diets also decreases plasma free fatty acid and cholesterol concentrations, and increases the number and activity of insulin receptors.

High fiber diets reduce insulin resistance. The fiber acts to decrease post prandial hyperglycemia, primarily because it delays gastric emptying. A high fiber diet also decreases absorption of glucose and increases insulin action at the receptor.

It has recently been suggested that diabetic cats be fed a high protein/low carbohydrate diet. This can be accomplished with several commercially available canned diets (Hill’s M/D, IVD Development, Purina DM, many other canned kitten diets). These diets may result in remission of the diabetes and elimination of the need for exogenous insulin and/or oral hypoglycemic agents. High protein/low carbohydrate diets more closely resemble the diet of felines in the wild and may help reduce glucose intolerance, insulin resistance and obesity.

**Feeding**

Ideally, the feeding schedule should be coordinated with the onset of action of the insulin. With dogs, this is fairly easy to regulate, but with cats, it is nearly impossible due to their "grazing" style of eating. For cat owners who may not be able to follow a strict feeding schedule or those with multiple pet households, insulin therapy will have to be adjusted to meet the owner's needs. The most important component of the dietary plan is to stress consistency in the diet. The following feeding schedule can be used for animals receiving insulin twice a day, feed four meals a day. Schedule them to coincide with the insulin injections and feed mid-afternoon and late evening.

If the owner is unable to follow this schedule, advise them to feed twice a day, at the time of injection and 8-10 hours later (for once a day insulin patients); or at the times of insulin injections (for twice a day insulin patients).

**Home management**

1. Instruct owner on proper injection techniques, injection locations, storage and handling of insulin.
2. Instruct owner on how to monitor clinical signs.
3. Continue feeding schedule and dietary therapy.
4. Instruct owners to initially monitor urine glucose/ketone levels daily, usually in the morning or evening prior to feeding. If persistent glycosuria or ketonuria is observed, ask owner to contact the veterinary hospital.
5. Advise owners of the signs of and treatment for hypoglycemia. Have owners keep a bottle of Karo syrup on hand if signs occur (i.e., weakness, ataxia, seizures) so they can rub syrup on the gums immediately. Instruct them to call the veterinary hospital.
6. Home monitoring of a diabetic cat is frequently based on observance of clinical signs only.
7. Serial sugars after the first week of home management.

**Re-check evaluations**

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1. Obtain owner assessment of clinical signs.
2. Serial blood sugars are helpful due to:
   a. Variability of insulin action in a given patient.
   b. Inaccuracy of random blood or urine sugars in monitoring the degree of glycemic control.
   c. Not particularly helpful as a routine procedure in animals that are well controlled clinically.
3. Body weight
4. Physical examination/ophthalmic exam
5. Discuss urine log book with owner
6. Laboratory work as clinically indicated
7. Role of glycosylated hemoglobin and fructosamine:
8. Fructosamine may be helpful in distinguishing stress-induced hyperglycemia from diabetes in cats. These tests can be used every 3 – 4 months as an indicator of long term (2-3 weeks fructosamine; 4-6 weeks glycosylated hemoglobin) glucose control. Rising values indicate the need for further evaluation.

Problems with insulin therapy
1. Insulin induced hyperglycemia (Somogyi phenomenon)
   a. Hypoglycemia (<65mg/dl) followed by hyperglycemia (>300mg/dl) within 24 hours of insulin injection.
   b. Suspect when insulin requirements exceed 2 U/kg and clinical signs persist.
   c. Suspect when animal has signs of hypoglycemia in afternoon.
   d. Diagnosis with serial sugars.
   e. Treat by decreasing insulin dose 25-50% and review insulin administration with the owner to rule out management problems.
   f. Re-check serial sugars in one week.
2. Rapid insulin metabolism
   a. Duration of insulin less than 18 hours.
   b. Signs return in the evening.
   c. Diagnosis is with serial sugars. Hyperglycemia (>250) within 18 hours of insulin injection without previous hypoglycemia.
   d. Treatment:
      e. -Review management with owner
      f. -Switch to twice daily insulin administration. Most dogs and cats require insulin twice a day to achieve adequate glycemic control. Consider switching to PZI in cats.
3. Insulin Resistance
   a. Hyperglycemia (>300) throughout the day, despite insulin dosages > 2 U/kg.
   b. Diagnosis based on serial sugars.
   c. Potential causes of insulin resistance:
      d. Management problems
      e. Hyperadrenocorticism
      f. Steroid or Ovaban administration
      g. Diestrus or pregnancy
      h. Acromegaly
      i. Concurrent illness, infection
      j. Anti-insulin antibodies
      k. Hypothyroidism (dogs), hyperthyroidism (cats)
   l. If insulin dose exceeds 2U/kg, the animal should be evaluated for one of these causes of resistance.
4. Hypoglycemia
   a. Insulin overdosage
   b. Suspect if animal shows weakness, shaking, ataxia, seizures at time of insulin’s peak effect.
   c. Therapy (instructions for owners)
   d. Mild signs - give food and call veterinarian
   e. Moderate signs - apply Karo syrup to the mouth, offer food when alert and then notify veterinarian.
   f. Comatose - apply Karo syrup to mouth and take animal to hospital.
   g. When hypoglycemia occurs, serial sugars should be performed to re-assess insulin dose
Insulin-Resistant Diabetes:
What to Do When Insulin Therapy Stops Working
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Insulin resistance is a condition in which a normal amount of insulin produces a suboptimal biologic response. Insulin resistance may result from problems occurring before the interaction of insulin with its receptor (e.g., insulin-binding antibodies), at the receptor (e.g., altered insulin receptor binding affinity or concentration), or at steps distal to the interaction of insulin and its receptor. Post-receptor problems are difficult to differentiate clinically from receptor problems, and both often coexist. In dogs and cats, receptor and post-receptor abnormalities are usually attributable to obesity, inflammation (such as occurs with pancreatitis or gingivitis), a disorder causing excessive secretion of a potentially insulin-antagonistic hormone (such as cortisol in dogs and cats or growth hormone and T4 in cats), or a disorder that causes a deficiency of hormone necessary for insulin action (such as thyroid hormone).

No insulin dose clearly defines insulin resistance. For most diabetic dogs and cats, control of glycemia can usually be attained using 1.0 U or less of NPH, lente insulin or glargine (cats) per kilogram of body weight given twice daily. Insulin resistance should be suspected if control of glycemia is poor despite an insulin dosage in excess of 1.5 U/kg, when excessive amounts of insulin (i.e., insulin dosage >1.5 U/kg) are necessary to maintain the blood glucose concentration below 300 mg/dL, or when control of glycemia is erratic and insulin requirements are constantly changing in an attempt to maintain control of glycemia. Failure of the blood glucose concentration to decrease below 300 mg/dL during a serial blood glucose curve is suggestive of but not definitive for the presence of insulin resistance. An insulin resistance-type blood glucose curve can also result from stress-induced hyperglycemia (cats), the Somogyi response, and other problems with insulin therapy, and a decrease in the blood glucose concentration below 300 mg/dL can occur with disorders causing relatively mild insulin resistance. Serum fructosamine concentrations are typically greater than 500 µmol/L in animals with insulin resistance and can exceed 700 µmol/L if resistance is severe.

Two diseases that have the potential to cause the most severe insulin resistance are hyperadrenocorticism and hypersomatotropism (acromegaly), although insulin resistance may also be mild or variable. Approximately 80% of cats with hyperadrenocorticism and nearly all cats with hypersomatotropism will develop diabetes mellitus. Hyperadrenocorticism is rare: 75% to 80% of cats have pituitary-dependent disease and 20% to 25% have cortisol secreting adrenocortical tumors. In rare circumstances, adrenocortical tumors secrete other steroid hormones (e.g., progesterone). However, clinical signs are identical to those of hypercortisolism, and diabetes mellitus may develop as well. In addition to PU/PD and weight loss, which are usually due to concurrent diabetes mellitus, typical clinical signs are abdominal enlargement, an unkept seborrheic hair coat, thinning of the hair coat, failure of hair to regrow, or alopecia and muscle weakness. Severe cases may have thin, fragile skin that tears easily. Cats with large pituitary masses may have CNS disturbances. However, clinical signs may also be mild and hyperadrenocorticism is often not suspected until it becomes evident that the diabetes is difficult to regulate. The dexamethasone suppression test is the preferred screening test. Whether poorly regulated diabetics do indeed have hyperactivity of the hypothalamus-pituitary-adrenal gland axis that leads to abnormal test results is controversial. Based on recent studies, the dexamethasone test (0.1 mg/kg dexamethasone IV with a pre, 4 and 8 hour post) appears to be a suitable part of the diagnostic workup in diabetic cats suspected of having hyperadrenocorticism and should be carried out only after insulin therapy has been instituted for 6-8 weeks to mitigate the effects of poor glycemic control on the HPA axis.

Hypersomatotropism in cats is caused by a growth hormone (GH)-producing tumor (usually an adenoma) in the pars distalis of the pituitary gland. GH has catabolic and anabolic effects; the latter are in part mediated by insulin-like growth factor-1 (IGF-1). The catabolic effects are mainly due to insulin antagonism and are the reason for the diabetes mellitus. The anabolic effects include proliferation of bone, cartilage, soft tissue, and organs resulting in a large body size, broad head and large paws, weight gain, prognathia inferior, respiratory difficulties because of thickening of pharyngeal tissues, degenerative arthropathy, and organomegaly with potential organ dysfunction. Growth of the tumor may lead to signs of CNS disease. As previously mentioned for hyperadrenocorticism, clinical signs may also be very subtle or even absent. Acromegaly has long been considered a rare disorder. However, it was recently suggested that acromegaly occurs more frequently than previously thought and is most likely underdiagnosed. Because the availability of a validated GH assay for cats is inconsistent, diagnosis is usually based on the finding of high IGF-1 concentration. Two important points should be kept in mind. First, circulating IGF-1 is bound to proteins, which must be removed before measurement. Not all assay methods are equally effective, and intra assay inference of binding proteins may lead to false high IGF-1 levels. Therefore, only assays validated for the cat should be used. Second, IGF-1 concentrations are often low in newly diagnosed diabetic cats and increase markedly after initiating insulin therapy. Low IGF-1 levels have also been seen initially in untreated diabetic cats with acromegaly. This observation is explained by the fact that relatively high insulin concentrations are required in the portal vein for the expression and function of GH receptors on hepatocytes, and this mechanism is impaired in insulin-deficient states. IGF-1 is therefore measured 6 to 8 weeks after initiating insulin therapy.
Problems with insulin therapy

- Inactive insulin
- Improper insulin syringe
- Diluted insulin
- Improper administration technique
- Inadequate dose
- Somogyi response
- Inadequate frequency of insulin administration
- Impaired insulin absorption
- Anti-insulin antibody formation (rare)

Caused by concurrent disorder

- Diabetogenic drugs
- Hyperadrenocorticism
- Diestrus (intact female dogs)
- Infection, especially of skin, oral cavity and urinary tract
- Chronic inflammation, especially pancreatitis and oral cavity
- Severe obesity
- Hyperlipidemia
- Hypothyroidism
- Hyperthyroidism (cat)
- Acromegaly (cat)
- Renal insufficiency
- Liver insufficiency
- Cardiac insufficiency
- Pancreatic exocrine insufficiency
- Neoplasia
- Glucagonoma
- Pheochromocytoma

Many disorders can interfere with the effectiveness of insulin therapy. The most common disorders causing insulin resistance in dogs include severe obesity, use of diabetogenic drugs (glucocorticoids), hyperadrenocorticism, diestrus, chronic pancreatitis, renal insufficiency, oral and urinary tract infections, hyperlipidemia, and antiinsulin antibodies in dogs receiving beef source insulin. Obtaining a complete history and a thorough physical examination are the most important steps in identifying these concurrent disorders. Abnormalities identified on the physical examination may suggest a concurrent insulin-antagonistic disorder or infectious process, which will give the clinician direction in the diagnostic evaluation of the dog. If the history and physical examination are unremarkable, a CBC, serum biochemical analysis, serum progesterone concentration (intact female dog), abdominal ultrasound, and urinalysis with bacterial culture should be obtained to further screen for concurrent illness. Additional tests will be dependent on results of the initial screening tests.

Diagnostic tests to consider for the evaluation of insulin resistance in diabetic dogs and cats

- Complete blood count, serum chemistry profile, UA and UMIC
- cPLI (pancreatitis)
- TLI (if suspect EPI)
- Adrenal Function Testing
  - Dexamathasone suppression test (cats)
- ACTH stimulation (likely less affected by concurrent diabetes in dogs)
  - Thyroid Function Testing
  - TT4
- fT4 (if TT4 is less than 1.5 ug/dl in a dog or between 2.5 – 4.0 ug/dl in a cat)
- Serum progesterone levels (diestrus in dogs)
- Serum IGF-1 concentrations (cats with suspected acromegaly)
- Fasting triglycerides and cholesterol
- Abdominal ultrasonography (pancreatitis, neoplasia, adrenal masses or enlargement)
- Thoracic radiographs (cardiopulmonary disease, neoplasia)
- MRI (if document PDH or acromegaly)
Hyperthyroidism is recognized as the most common endocrinopathy of older cats. Despite worldwide occurrence, the pathogenesis of feline hyperthyroidism remains unclear. Traditional methods of managing feline hyperthyroidism include thyroidectomy, anti-thyroid medications, and radioactive iodine. Recent studies document that another option now exists for hyperthyroid cats; feeding a limited-iodine food normalizes thyroid hormone concentrations and alleviates clinical signs of hyperthyroidism. Surgery and radioactive iodine are designed to provide permanent solutions, whereas, oral anti-thyroid drugs and nutritional management control hypothyroidism and are needed daily to achieve/maintain their effect. All management options are effective and each has its pros and cons. It’s important to discuss all options with pet owners so the appropriate management can be selected for each hyperthyroid cat.

**Diagnosis**

Diagnosis most often is based on the presence of one or more typical clinical signs and increased serum total thyroxine (T4) concentration. However, up to 10% of all hyperthyroid cats and 40% of those with mild disease have serum T4 values within reference range. In these cases, serum free T4 (fT4), measured by equilibrium dialysis, may provide an alternative means of diagnosing hyperthyroidism in cats with normal serum total T4 values. Studies document that up to 20% of sick euthyroid cats can have increased fT4 concentration. Therefore, it is most appropriate and reliable to interpret the two values together. Mid-to-high reference range total T4 and increased fT4 concentration is consistent with hyperthyroidism. In contrast, low total T4 and increased fT4 values are usually associated with non-thyroidal illness.

**Management options**

Once hyperthyroidism has been diagnosed, all management options (thyroidectomy, radioactive iodine, anti-thyroid drugs, nutritional management) should be discussed with pet owners. All options can be ≥ 90% effective for controlling hyperthyroidism when used appropriately. The selected management option will differ for each cat based on several considerations. Radioactive iodine therapy is considered the gold standard for treatment of hyperthyroidism; however, most pet owners currently opt for medical management. Until recently, this included oral or transdermal anti-thyroid drugs. Now nutritional management using a limited-iodine food is another option for cats with hyperthyroidism.

**Radioactive iodine**

Radioiodine treatment is often considered the best option for many hyperthyroid cats because:

1. It has the potential to eliminate a benign thyroid tumor or abnormal thyroid tissue with a single treatment
2. It treats extra-thyroidal thyroid tissue, which may occur in 10 to 20% of hyperthyroid cats
3. No general anesthesia is required
4. Reported side effects are minimal

Cats should be stable prior to radioiodine therapy; those with clinically significant cardiovascular, renal, gastrointestinal, or endocrine (e.g., diabetes mellitus) disease may not be very good candidates, especially because of the time necessary for boarding after treatment.

After administration, radioactive iodine is actively concentrated by the thyroid gland and has a half-life of 8 days. It emits both β-particles and γ-radiation; the β-particles are responsible for the majority of tissue destruction, but are only locally destructive, traveling a maximum of 2 mm. Therefore, no significant damage to adjacent parathyroid tissue, atrophic thyroid tissue, or other cervical structures is expected. The main limitation to widespread use of radioactive iodine is the requirement for special licensing and the isolation of the cat for variable periods after treatment. This can range from several days to several weeks depending on state or local radiation regulations and the dose administered.

The goal of treatment is to restore euthyroidism with the smallest possible single dose of radioactive iodine, while avoiding development of hypothyroidism. Controversy exists as to the best method of calculating the optimum dose for individual cats. Based on the majority of reported cases, post-treatment hypothyroidism is transient and generally uncommon (2 to 7% of cases); even fewer cats have clinical signs or appear to require thyroid hormone replacement. However, up to 30% (50 of 165 cats) were hypothyroid 3 months after radioactive iodine therapy in one study; of these, 56% (19 of 34 hypothyroid cats with available information) had clinical signs of hypothyroidism and 52% (23 of 44 cats) were given thyroid hormone supplementation. Thyroid hormone replacement may be needed in some cats, especially those with concurrent kidney disease, since hypothyroidism has been associated with azotemia and decreased survival time in previously hyperthyroid cats. Owners should be advised of this possibility, particularly if their motivation is to avoid long-term oral medication.
Anti-thyroid drugs

Anti-thyroid drugs (e.g., methimazole, carimbazole) are commonly used for treatment of hyperthyroidism in cats. If administered appropriately, they reliably inhibit the synthesis of thyroid hormones and thereby lower serum thyroid hormone concentrations. These drugs do not affect the thyroid gland’s ability to trap inorganic iodide or release preformed hormones. They are widely recommended to stabilize hyperthyroid cats prior to surgery and are the only drugs that can be used chronically for management of hyperthyroidism. Almost all cats are potential candidates unless thyroid carcinoma is suspected.

Anti-thyroid drugs used most often in cats include methimazole and carimbazole; both can be given orally or formulated for transdermal application. Custom formulation of transdermal products may increase expense of therapy and stability of the product is not guaranteed. Results of a recent prospective study conducted in New Zealand showed that once daily treatment for 12 weeks with transdermal methimazole in a novel lipophilic vehicle was as effective as twice-daily carimbazole administered orally.

While many cats have been successfully managed long-term with anti-thyroid drugs, it’s important to monitor for potential side effects that have been associated with their use. In the study with the largest number of cats, 18% had side effects associated with methimazole; a more recent study revealed that 44% of 39 cats had side effects. In 44 cats receiving carimbazole for 1 year, 44% had associated side effects with gastrointestinal signs (decreased appetite, vomiting, diarrhea) being most common. In another study, 13% of 39 cats treated with carimbazole experienced side effects. It’s difficult to determine what % of side effects are caused by the drug versus something else such as concurrent disease.

Most adverse reactions occur within the first few weeks to months after beginning therapy and include depression, inappetence, vomiting, and self-induced excoriations of the head and neck (facial pruritus). Gastrointestinal signs are less common with transdermal administration of methimazole. Mild to serious hematological complications, including agranulocytosis and thrombocytopenia either alone or concurrently, and more rarely immune-mediated hemolytic anemia may also occur. Hepatic toxicity with marked increases in bilirubin concentration and hepatic enzyme activities has been described in less than 2% of cats treated with methimazole. Cessation of therapy is required if either serious hematologic or hepatic reactions develop. Serum antinuclear antibodies develop in approximately 50% of cats treated with methimazole for longer than 6 months, usually in cats on high-dose therapy (> 15 mg/day). Although clinical signs of a lupus-like syndrome have not been reported, decreasing the daily dosage is recommended.

Nutritional management

Production of thyroid hormone requires uptake by the thyroid gland of sufficient amounts of iodine, which is provided by dietary intake. The only function for ingested iodine is for thyroid hormone synthesis. This observation led to the hypothesis that limiting dietary iodine intake could be used to control thyroid hormone production and potentially manage hyperthyroidism in cats. After more than a decade of research and development, a limited-iodine therapeutic food (Hill’s® Prescription Diet® y/d Feline) containing < 0.3 ppm (mg/kg) iodine on a dry matter basis (DMB), is now available as an option for managing cats with hyperthyroidism.

Iodine content of commercial cat foods

Iodine occurs naturally in many ingredients typically used in the manufacture of commercial pet foods (particularly fish, shellfish and fresh meats) and unless steps are taken to strictly control the iodine content of ingredients, the final iodine concentration in pet foods varies widely. Commercial cat foods in New Zealand had iodine amounts ranging from 0.19 to 21.2 ppm in one study whereas in Germany a range of 0.22 to 6.4 ppm was reported. Evaluation of 28 canned cat foods in the US revealed an iodine content ranging from 1.09 to 52.3 ppm (mean = 7.83) and 14 dry cat foods contained iodine amounts ranging from 1.34 to 5.94 ppm (mean = 2.77). Based on these studies, the amount of iodine is much higher in many canned foods compared with dry foods and variability of iodine content is much greater in canned food.

Multiple feeding trials have been conducted in a research colony using over 100 cats with naturally occurring hyperthyroidism to determine the safety and effectiveness of limited dietary iodine in the management of the disease. The results of all studies support that a therapeutic food with dietary iodine ≤ 0.3 ppm iodine (dry matter basis) provides a safe and effective management option for cats with naturally occurring hyperthyroidism. Serum total thyroxine concentrations return to the normal range within 4 to 12 weeks of initiating nutritional management and 90% hyperthyroid cats maintained on the limited-iodine food as the sole source of nutrition become euthyroid.

Three studies were designed to determine the magnitude of iodine control necessary to return newly diagnosed cats to a euthyroid state, the maximum level of dietary iodine that maintains cats in a euthyroid state, and the effectiveness of a therapeutic food formulated based on the previous studies to control naturally occurring hyperthyroidism in cats. In summary, results of these studies demonstrated that a food with 0.17 or 0.32 ppm iodine (DMB) maintained normal thyroid hormone concentrations in hyperthyroid cats, helping to further define the range of iodine effective for managing hyperthyroidism.

We have treated 22 cats to date with feline y/d with follow-up data for at least 6 months. All of the cats found at least one form of the diet (dry or canned) to be palatable. Nineteen of 22 (86%) cats experienced clinical improvement with normalization of their TT4 concentrations. Of the three cats that failed to achieve remission, 2 cats were discovered to be eating foods other than y/d and when
the owners switched them to y/d exclusively remission of hyperthyroidism was achieved. One cat (5%) failed to respond to dietary therapy and was subsequently treated with 131-I.

We are currently conducting a prospective study evaluating the efficacy of feline y/d in managing feline hyperthyroidism to include monitoring of thyroid function (TT4, fT4ED, TSH), clinical signs, body weight, renal function and blood pressure pre and post-treatment. The study should be completed in 2015.

Newly diagnosed patients
After confirming the diagnosis and performing a thorough patient evaluation, nutritional management should be discussed along with other options for managing hyperthyroidism. If selected as the management option, gradual transition to the limited-iodine food (Hill’s® Prescription Diet® y/d Feline) over at least 7 days is recommended. It is very important to counsel owners so they understand that success of nutritional management depends on the limited-iodine food being the sole source of nutrition for their cat.

The first recheck evaluation should be done 4 weeks after completing the transition to y/d Feline (i.e., once the cat has eaten y/d exclusively for 4 weeks) and as a minimum should include physical examination and measurement of T4, BUN, serum creatinine, and urine specific gravity. All cats should have decreased T4 concentrations compared with baseline and many will have returned to normal by the 4-week evaluation. Clinical improvement including weight gain, improved hair coat and decreased tachycardia/cardiac murmur also may be noted by the first evaluation. Clinical signs should continue improving by the next re-evaluation at 8 weeks and most cats will be euthyroid. Some cats require slightly longer to become euthyroid; however, it’s expected that 90% will have normal T4 concentrations if the limited-iodine food is their sole source of nutrition.

If euthyroidism is not achieved within 4 to 12 weeks, a thorough history is indicated to confirm that only the limited-iodine food is being fed.

Managing hyperthyroid cats with concurrent kidney disease
Chronic kidney disease (CKD) and hyperthyroidism are more likely to be diagnosed in older cats so it’s not surprising that many hyperthyroid cats have CKD. Untreated hyperthyroidism complicates the diagnosis of CKD because it’s associated with increased glomerular filtration rate (GFR) and therefore often masks biochemical markers of CKD. Regardless of the therapeutic modality (methimazole, surgical thyroidectomy, or radioiodine), decreased GFR, increased serum urea and creatinine concentrations and development of overt clinical signs of kidney disease have been reported after successful treatment of hyperthyroidism. The presence of underlying CKD may affect the prognosis - one study documented a shorter survival time in hyperthyroid cats with azotemia. However, two recent studies comparing survival of cats that developed azotemia with those that did not after treatment of hyperthyroidism found no significant difference between the two groups if cats did not become hypothyroid post-treatment.

The reported occurrence of azotemia after treatment of hyperthyroidism ranges from 15 to 49%. Iatrogenic hypothyroidism has been reported to decrease GFR in human patients. Post-treatment iatrogenic hypothyroidism has been reported in cats after radioiodine therapy and bilateral thyroidectomy, which constituted the predominant therapeutic modalities in previous studies. In one recent study, cats with iatrogenic biochemical hypothyroidism were almost twice as likely to develop azotemia post-treatment as euthyroid cats. The hypothyroid cats with azotemia had shorter survival times than cats without azotemia, whereas, consistent with previous reports, there was no difference in survival times of euthyroid cats with or without azotemia.

It’s not possible to consistently predict which cats will develop overt CKD after treatment of hyperthyroidism or have progression of their kidney disease. This should be considered when deciding on treatment options, particularly those that are irreversible (thyroidectomy, radioactive iodine). Regardless of the option selected for managing hyperthyroidism, it’s important to remember that the only intervention shown to improve quality of life and prolong survival time in cats with naturally occurring CKD is feeding a therapeutic renal food. Until recent availability of limited-iodine food, nutritional recommendations have not generally been considered for hyperthyroid cats without azotemia. In cats with compromised renal function, but without azotemia (IRIS Stage 1), the decrease in GFR associated with normalizing serum T4 levels may be sufficient to prevent effective clearing of protein metabolic by-products (BUN and creatinine) when dietary intake of protein and phosphorus is high. This could contribute to the occurrence of post-therapy azotemia in hyperthyroid cats.

In our work with 22 cats with hyperthyroidism treated with feline y/d, 4/22 cats (18%) were azotemic (IRIS Stage 1 and 2 CKD) prior to starting the diet. All 4 cats experienced normalization of their BUN and creatinine within 30-150 days along with normalization of their TT4’s. One potential explanation is that the expected decrease in GFR associated with normalizing serum T4 may be offset by the nutrient profile of the limited-iodine food which is similar foods for mature adult cats or cats with early CKD. Additional study is needed to better understand the effects of using limited-iodine food on hyperthyroid cats with concurrent kidney disease.

Conclusions/summary
Hyperthyroidism is the most common endocrine disease of older cats worldwide. While the pathogenesis is unclear, several effective management options are available. All should be discussed with pet owners, including pros/cons, so that the best option can be
selected for individual patients and their owners. Feeding a limited-iodine food is now available as an option for effective management of hyperthyroid patients. When fed as the sole source of nutrition, approximately 90% of hyperthyroid cats become euthyroid within 4 to 12 weeks. To date, over 150 cats with naturally occurring hyperthyroidism have been managed successfully by feeding a limited-iodine food, most for 2-3 years and some cats for as long as 6 years.
Solving the Puzzles of Puddles: PU/PD

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Introduction
A. Polyuria and polydipsia (PU / PD) refer to excessive water consumption and urine production respectively. These are common clinical signs in both dogs and cats.
B. Water consumption exceeding 100 ml/kg or urine production exceeding 50 ml/kg body weight per day is considered abnormal and should be pursued. These numbers have been established in laboratory reared dogs and may not reflect "normal" water consumption in pets. They are to be used only as guidelines.
C. Water consumption can vary greatly from day to day so it is important to have owners subjectively assess water consumption in the home environment for several consecutive days in order to obtain an accurate picture before beginning unnecessary and expensive diagnostic tests. Actual quantification of water consumption can be very difficult and may not be practical for the majority of pet owners.

Normal water homeostasis
A. Extracellular fluid volume is maintained by regulation of fluid intake and urine production.
B. The thirst center is stimulated by an increase in plasma osmolality (sodium concentration) and/or a decrease in blood volume (hypovolemia) resulting in an increase in water consumption.
C. Increasing plasma osmolality and hypovolemia also stimulate osmoreceptors in the anterior hypothalamus and baroreceptors in the aortic arch resulting in the release of antidiuretic hormone (ADH) from the anterior pituitary.
D. ADH circulates and binds to receptors on the renal tubular cells of the distal tubules and collecting ducts resulting in the production of cAMP. This causes the opening of pores in the luminal membrane of the tubular cells and allows for reabsorption of water from the glomerular filtrate resulting in a concentrated urine. In order for water to be pulled out of the tubule it must move along a concentration gradient maintained by the hypertonic renal medullary interstitium. Loss of this gradient (medullary washout), will result in an inability to concentrate urine even in the face of normal ADH activity. Urea and sodium are largely responsible for maintaining the hypertonicity of the interstitium.
E. The sensation of thirst and secretion of ADH are suppressed when plasma osmolality and blood volume are returned to normal.

Differential diagnosis: Mechanisms of PU/PD
A. Renal disease:
   a. Chronic renal failure: A decrease in the number of functional nephrons causes an increase in tubular flow in the remaining nephrons and leads to a solute diuresis. A decrease in urine concentrating ability may be the only laboratory abnormality indicating renal disease (especially in feline patients) presented for PU/PD.
   b. Pyelonephritis: Bacterial induced tubular destruction and an increase in renal blood flow cause a decrease in medullary hypertonicity.
   c. Primary renal glycosuria (Fanconi's Syndrome): A proximal tubular defect results in renal glycosuria leading to an osmotic diuresis. The blood glucose is normal.
   d. Post-Obstructive diuresis: May be seen in previously blocked cats. Due to osmotic diuresis from loss of large amounts of sodium and urea into the urine following relief of urethral obstruction.
B. Diabetes mellitus:
   a. Hyperglycemia results in glycosuria and an osmotic diuresis. Threshold for renal glycosuria is a blood glucose of 180 – 220 mg/dl (dog) and 240 – 300 mg/dl (cat).
C. Liver disease:
   a. PU/PD may occur as the result of: (1) decreased production of urea which is a major component of the hypertonic medullary interstitium, (2) increased renin and cortisol levels due to a lack of hepatic degradation, (3) increased aldosterone concentration leading to increased sodium concentration, and (4) hypokalemia (see hypokalemic nephropathy).
D. Hyperthyroidism:
   a. Increased total renal blood flow reducing the tonicity of the medullary interstitium.
   b. Psychogenic polydipsia or primary polydipsia is reported in humans with hyperthyroidism.
E. Hypercalcemia:
a. Interference with cAMP activation by ADH, damage to ADH receptors, and mineralization of renal tubular cells.

F. Hyperadrenocorticism:
   a. Glucocorticoids interfere with the action of ADH at the renal tubule and decrease ADH secretion by reducing osmoreceptor sensitivity to rising plasma osmolality.

G. Hypoadrenocorticism:
   a. Renal sodium wasting leads to decreased medullary hypertonicity.

H. Pyometra:
   a. coli endotoxins interfere with sodium reabsorption and damage ADH receptors and may result in an immune-complex glomerulonephritis.

I. Hypokalemia:
   a. Degeneration of renal tubular cells, (2) decreased medullary hypertonicity, stimulation of thirst, and (4) stimulation of renin release.

J. Polycythemia:
   a. Mechanism unknown; may be related to sluggish blood flow in kidney or hypothalamus.

K. Medications:
   a. Exogenous steroids, diuretics, salt supplementation, primidone, phenobarbital, KBr and vitamin D.

L. Pituitary or central diabetes insipidus (CDI):
   a. Due to inadequate production, storage or release of ADH. May occur as a congenital defect or secondary to trauma, mass lesions, infection or infarction of the pituitary or hypothalamus.

M. Nephrogenic diabetes insipidus (NDI):
   a. Congenital structural or functional defects in ADH receptor. Rare in dogs and cats.

N. Primary polydipsia or psychogenic polydipsia:
   a. Underlying cause unknown (possible CNS lesion); results in increased renal blood flow and a decrease in medullary hypertonicity. Extremely uncommon in dogs and cats and is largely a diagnosis of exclusion.

**Diagnostic approach to PU / PD**

A. Document PU/PD actually exists. Recommend assessment of water consumption in the home environment. Hospitalized animals frequently do not drink as much as they would in their natural surroundings.

B. Quick evaluation of urine specific gravity and glucose is cheap, easy, and very helpful in evaluating animals for possible pathologic PU/PD. If the urine specific gravity of a non-glycosuric sample, obtained from a dog or cat without signs of dehydration, is greater than 1.030 (dog) or 1.035 (cat), the likelihood of pathologic PU/PD is small and further work-up may not be required.

C. Most causes of PU/PD will be identified following a good history, physical examination, and an initial data base consisting of a CBC, chemistry profile, and urinalysis with bacteriologic culture.

D. If a cause has not been discovered after step C, the most likely diagnoses are hyperadrenocorticism (dog only, cats with Cushing's are usually overtly diabetic), central and nephrogenic diabetes insipidus, and primary polydipsia. As hyperadrenocorticism is far more common than either of the other causes, an ACTH stimulation test, urine cortisol/creatinine ratio or low-dose dexamethasone suppression test should be performed before proceeding to the modified water deprivation test (See Canine Hyperadrenocorticism).

**Modified water deprivation test (MWDT)**

A. This test is designed to help differentiate CDI, NDI, and primary polydipsia. It is not very helpful unless other causes of PU/PD have been ruled out.

B. The test is designed to determine whether ADH is released in response to dehydration and whether the kidneys can respond to the circulating ADH.

C. **VERY IMPORTANT!!! THE TEST SHOULD NEVER BE PERFORMED ON AN ANIMAL WITH PRE-EXISTING AZOTEMIA OR OBVIOUS DEHYDRATION. DOING SO IN ANIMALS WITH RENAL INSUFFICIENCY MAY RESULT IN DECOMPENSATION AND THE DEVELOPMENT OF OLIGURIC RENAL FAILURE OR ANURIC RENAL FAILURE.**

D. Severe dehydration can occur very rapidly (4-6 hours) especially in animals with diabetes insipidus. Leaving them unattended without water for several hours or overnight may result in severe hyperosmolality, coma, and death.

E. Gradual water restriction should be instituted at home for 2-3 days prior to performing the MWDT in order to help minimize medullary washout from long-standing PU/PD.
Phase one
1. Animal is weighed, bladder emptied and urine saved for specific gravity and osmolality (if available).
2. Blood is obtained for BUN and osmolality.
3. Water is withheld. BUN, plasma osmolality and body weight are obtained hourly. The bladder is emptied every hour and a sample is saved for specific gravity and osmolality.
4. Test concluded with either a 5% loss in body weight, azotemia (BUN > 30), or urine specific gravity > 1.030 (1.035 cats). The bladder is emptied and urine is saved for specific gravity and osmolality, and plasma is obtained for osmolality.

Phase two
1. Aqueous vasopressin (Pitressin) 2 - 3 units (dog) or 0.25 U/# (cat) is given SQ. Alternatively DDAVP may administered into the conjunctival sac (1 – 2 drops for dogs and 1 drop for cats).
2. Urine and plasma osmolality and urine specific gravity are obtained every 30 min for 90 minutes.
3. Bladder must be emptied at every 30 minute sampling period.
4. Water is withheld throughout the test.

Interpretation of the MWDT
A. Normal Animals: Following water deprivation will concentrate urine to > 1.030 (dog) or 1.035 (cat). Urine osmolality in excess of 1,200 mOsm/kg.
B. CDI: Unable to concentrate urine in excess of 1.008 (< 300 mOsm/kg). After ADH administration, urine specific gravity should increase to greater than 1.012 with a 50 - 500 % increase in urine osmolality.
C. NDI: Similar to CDI following water deprivation. No further response following ADH injection.
D. Partial CDI: Results depend on how much ADH is available. Following water deprivation urine specific gravity between 1.008-1.019 and urine osmolality between 300 to 1,000 mOsm/kg. Urine specific gravity and osmolality increase after ADH administration. Similar response seen with hyperadrenocorticism and a number of the other causes of PU/PD. This is why it is important to rule-out these processes prior to a MWDT.
E. Primary polydipsia: Depends on degree of medullary washout. With minimal washout results are similar to normal animals. More severe washout gives results similar to partial diabetes insipidus.

Treatment of polyuria and polydipsia
A. Treat the underlying disorder!
B. Treatment of CDI
   a. DDAVP (Desmopressin acetate) 1-2 drops into the conjunctival sac or 0.01 to 0.05 mls subcutaneously SID or BID. May also dose orally with 0.1 to 0.2 mg once or twice a day.
      i. 1 drop = 1.5 to 4.0 ug. Can use TB syringe to dose.
      ii. Duration 8 - 24 hours.
      iii. Redosed when polyuria returns.
      iv. Most commonly used treatment today.
      v. Use the intranasal preparation.
   b. Chlorpropamide (Diabenese)
      i. Oral hypoglycemic. Stimulates ADH release and potentiates ADH action. Hypoglycemia is the limiting factor.
      ii. 25 - 40 mg once or twice a day (cat). Limited experience.
C. Treatment of NDI
   a. Salt restriction
   b. Thiazide diuretics:
      i. Natriuresis results in a decrease in blood volume and increased sodium reabsorption in the proximal tubule.
      ii. Hydrochlorothiazide 12.5 - 25 mg once or twice a day (cat).
      iii. Chlorthiazide 20 - 40 mg/kg BID (dogs).
      iv. May also help with partial CDI.
D. Treatment of Primary Polydipsia
   a. Treatment to restore hypertonic renal medullary interstitium.
   b. Gradual water restriction over several days.
   c. Behavioral modification or referral to a behaviorist may be needed.
The Art and Joy of Identifying and Treating Canine Hyperadrenocorticism
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1. Introduction
   - Cushing's syndrome refers to all causes of hyperadrenocorticism with overproduction of cortisol.
     - ACTH-dependent
       - Cushing's disease: Pituitary hypersecretion of ACTH which results in bilateral adrenal hyperplasia (90% of cases)
       - Ectopic ACTH production: Non-pituitary tumors secreting ACTH resulting in bilateral adrenal hyperplasia. Has not been completely documented in dogs or cats.
     - ACTH independent
       - Adrenocortical adenoma or carcinoma: Hypersecretion of cortisol with atrophy of normal adrenal and suppressed ACTH concentrations (10% of cases).
     - Iatrogenic
       - Excessive or prolonged administration of glucocorticoids. Clinically indistinguishable from natural disease. Results in adrenal atrophy and suppressed ACTH levels.

2. Signalment
   - Poodles, Dachshunds, Schnauzers, Boston Terriers, Boxers.
   - Middle to old age. Average 12 years; range 6 months to 17 years.
   - No sex predilection.
   - Rare in cats. Usually seen with insulin resistant diabetes mellitus and/or cats with severe dermal atrophy/ulceration.

3. Clinical signs
   - PU / PD
   - Pendulous, "pot-bellied abdomen": Due to muscle catabolism by glucocorticoids and hepatomegaly.
   - Bilaterally symmetric alopecia: Head and extremities spared.
   - Thin skin
   - Muscle weakness and muscle atrophy; cruciate ruptures
   - Mineralization of skin (calcinosis cutis)
   - Hyperpigmentation: ACTH similar to MSH, co-existing hypothyroidism, chronic skin irritation.
   - Reproductive abnormalities
     - Anestrus
     - Clitoral hypertrophy
     - Testicular atrophy
     - Perianal adenomas in females and neutered males.
   - Respiratory signs
     - Panting: Pulmonary hypertension and decreased compliance, primary CNS disturbance, pulmonary mineralization.
     - Dyspnea: Rare; seen with pulmonary thromboembolism and concurrent congestive heart failure.
   - Central nervous system
     - Seen with large pituitary tumors (macroadenomas). Present at time of diagnosis or following therapy for Cushing's disease as microscopic pituitary tumors enlarge into macroadenomas.
     - Signs due to compression/invasion of pituitary and/or hypothalamus:
       - Seizures
       - Pacing
       - Lethargy
       - Inappetence
       - Behavior change
       - Head pressing
       - Circling
4. Diagnosis of hyperadrenocorticism

- History and clinical signs
  - R/O iatrogenic disease with questions concerning current or past medications. These medications can include oral, ophthalmic, otic, and topical medications. Make sure the owner tells you about everything and anything that went on or in their pet.
- Laboratory data
  - Hemogram
    - Polycythemia (PCV 45-55%)
    - Stress leukogram
      - Lymphopenia
      - Eosinopenia
      - Neutrophilia (mature)
  - Biochemistry profile
    - Elevations in:
      - Serum alkaline phosphatase (SAP)
      - Cholesterol
      - Serum alanine aminotransferase (ALT)
      - Fasting blood glucose: Diabetes in 5-10%.
  - Thyroid function tests
    - T3 and T4 basal levels are generally decreased.
    - Response to TSH parallels normal.
    - Secondary to negative feedback of cortisol on pituitary.
    - 80% have a normal FT4ED
    - Does not require thyroid supplementation.
  - Blood pressure: 50 – 80% are hypertensive, cause unknown.
    - Recent study demonstrated normal or decreased levels of atrial natriuretic factor (ANF) in dogs with hyperadrenocorticism. Argues against hypervolemia as the etiology of the hypertension.
  - Urinalysis
    - Decreased urine specific gravity.
    - Proteinuria
- Radiographic abnormalities
  - Thoracic films
    - Bronchial calcification
    - Metastases from adrenal adenocarcinoma
  - Abdominal films
    - Hepatomegaly
    - Osteopenia
    - 50% of adrenal tumors are visualized as soft tissue or calcified masses.
    - Subcutaneous calcification
- Adrenal function tests
  - Three tests used to diagnose hyperadrenocorticism. They do not differentiate between PDH or AT.
    - ACTH stimulation test
      - Look for exaggerated cortisol response in response to ACTH.
      - See protocols at the end of this discussion.
      - Diagnostic in 85% of pituitary-dependent cases (PDH)
      - Diagnostic in 70% of adrenal tumors (AT)
      - Overall accuracy 80-85%
      - A suppressed response to ACTH in animals with clinical signs of hyperadrenocorticism suggests iatrogenic disease.
  - Low-dose dexamethasone suppression test
    - Low doses of dexamethasone inhibit ACTH release from the pituitary via negative feedback and decrease plasma cortisol concentrations in normal dogs.
    - Dogs with Cushing's are more resistant to steroid suppression. Therefore, lack of suppression following dexamethasone = hyperadrenocorticism.
- Diagnostic in 95% of PDH
- Diagnostic in 100% of AT
- Overall 90-95%
- May also be used to distinguish PDH from AT (see below)
- See protocols

- Urine cortisol/creatinine ratio
  - Assessment of cortisol production and excretion rate.
  - Sensitivity of this test is greater than that of the LDDS (some animals with clinical signs of hyperadrenocorticism may have normal LDSD response tests but elevated urine cortisol to creatinine ratios). Used as a screening test.
  - Test is easy to perform.
  - As with all adrenal function tests, elevated results may occur in animals with non-adrenal disease.
  - Positive tests confirmed with a LDSD.
  - Must be performed on urine obtained at home, preferably in the AM

- Tests to differentiate PDH from AT (performed after confirming diagnosis of hyperadrenocorticism).
  - High-dose dexamethasone suppression test
    - With PDH, a high dose of dexamethasone results in a decrease in ACTH release from the pituitary and a decrease in plasma cortisol.
    - With AT, the tumor secretes cortisol autonomously thereby suppressing ACTH production. With low ACTH concentrations already present, dexamethasone has no effect on plasma cortisol.
    - 70% of patients with PDH suppress plasma cortisol to less than 50% of the pre-treatment value.
    - 100% of patients with AT do not suppress.
    - Therefore: Suppression = PDH; Lack of suppression = Inconclusive
    - See protocol
  - Endogenous ACTH concentration
    - PDH: Levels normal or high
    - AT: Levels low to undetectable
    - Contact lab regarding sample handling and collection. Use of the preservative (Aprotinin) allows for greater utilization of this test.
    - Excellent method to differentiate PDH from AT.

Testing protocols
These are suggested protocols that are used in the evaluation of patients with hyperadrenocorticism. You must use the protocol and normal values from the laboratory to whom you are submitting samples to properly evaluate endocrine tests.

- ACTH Stimulation Test
  - Synthetic ACTH (Cortrosyn) 5 ug/kg IV or IM; collect serum at 0 and 1 hour, or
  - ACTH gel (Acthar) 2.2 U/kg IM; collect serum at 0 and 2 hours.
  - Hyperadrenocorticism if post-cortisol > 20 ug/dl (530 nmol/L)

- Low-Dose Dexamethasone Suppression Test
  - 8 A.m: Baseline serum cortisol. Administer 0.01 mg/kg dexamethasone sodium phosphate (0.015 mg/kg dexamethasone) IV.
  - 12 p.m: Collect 4 hour post-dexamethasone cortisol.
  - 4 p.m: Collect 8 hour post-dexamethasone cortisol.
  - In normal animals cortisol suppresses to less than 1.0 ug/dl (27.5 mmol/L) at 8 hours.
  - 50% or greater suppression at either 4 or 8 hours together with lack of suppression at 8 hours is diagnostic for PDH and additional tests are not necessary.

- Urine Cortisol/Creatinine Ratio
  - First morning urine sample is preferred. Sample should be obtained at home. Requires 1 – 2 mls.
  - Stable at room temperature or refrigerated for 3 days.
  - Normal range 2.8 - 4.8. A normal result effectively rules-out hyperadrenocorticism, an abnormal result should be confirmed with a LDSS or ACTH stimulation test.

- Differentiating PDH From AT
  - Low-Dose Dexamethasone Suppression Test
    - See above.
  - High-Dose Dexamethasone Suppression Test
- 8 a.m: Obtain serum cortisol. Administer 0.1 mg/kg dexamethasone sodium phosphate (0.15 mg/kg dexamethasone) IV.
- 4 p.m: Collect post-dexamethasone cortisol.
- Suppression defined as greater than a 50% reduction of cortisol.
- Suppression = PDH, non-suppression = Inconclusive

  o Endogenous ACTH Concentration
    - Check with lab on sample collection and handling.
    - Normal: 20-100 pg/ml (4.4-22.0 pmol/L)
    - PDH: 40-500 pg/ml (8.8-110 pmol/L)
    - AT: < 20 pg/ml (<4.4 pmol/L)

Treatment options

A. Pituitary-dependent hyperadrenocorticism

1. Surgical management
   a. Bilateral adrenalectomy
      i. Technically difficult
      ii. Poor surgical/anesthetic risk
      iii. Permanently hypoadrenal and require lifelong replacement therapy
   b. Hypophysectomy
      i. See discussion at the end of this section
      ii. Lifelong therapy with thyroid hormone and prednisone necessary.

2. Medical therapy

Prognosis

Most dogs with PDH live normal lives (average 2.2 years, but remember most are geriatric to begin with.)

1. Complications
   a. Recurrence of disease.
   b. CNS signs.
   c. Pulmonary thromboembolism.
   d. Infections.
   e. Hypertension.
   f. Congestive heart failure.

2. Adrenal tumors:
   a. Adenomas: Good if no evidence of local invasion.
   b. Carcinomas: Guarded to grave with metastases.

Trilostane therapy of canine hyperadrenocorticism

The efficacy and safety of trilostane in the treatment of canine PDH were evaluated in a multicentre study at the Royal Veterinary College in London, the Veterinary Teaching Hospital in Dublin and Small Animal Hospital in Glasgow. Seventy-eight dogs with confirmed PDH were treated with trilostane for up to 3 years. The starting dose varied from 1.8 to 20 mg/kg (mean = 5.9 mg/kg).

Trilostane appeared to be well tolerated by almost all dogs with only 2 dogs developing signs and biochemical evidence of hypoadrenocorticism. One of these dogs recovered with appropriate therapy. The other died despite withdrawal of trilostane and administration of appropriate therapy. A further two dogs died within one week of starting trilostane but in neither case could a direct link with the trilostane therapy be established. The low prevalence of side effects compared favourably to those reported with mitotane.

Trilostane was found to be nearly as effective as mitotane in resolving the signs of hyperadrenocorticism. Polyuria, polydipsia and polyphagia had dissipated in 40 dogs within 3 weeks after starting trilostane. Within 2 months, a further 20 dogs showed decreases in their water and food consumption. These improvements were maintained as long as the dogs remained on adequate doses of trilostane. Skin changes resolved in 24 out of 39 (62%) of dogs that initially presented with dermatological signs. All of these improvements were maintained as long as the dogs remained on adequate doses of trilostane. Only 8 dogs that were treated with trilostane for more than 2 months showed poor control of clinical signs. In contrast, mitotane is effective in about 80% of cases of pituitary dependent hyperadrenocorticism (PDH).

Trilostane caused a significant (p<0.001) reduction in both the mean basal and post-ACTH stimulation cortisol concentrations after 10 days of treatment. The post ACTH cortisol concentration decreased to less than 250 nmol/l (9 µg/dl) in 81% of dogs within one
month and in another 15% at some time whilst on treatment. These improvements were also maintained in the study population for the duration of the trial.

Thirty-five dogs had at least one dose adjustment over the treatment period. The dose was increased in 23 dogs up to four times the starting dose. In one dog the dose was increased nine fold over a period of six months. The dose was decreased in nine dogs to as low as a quarter of the starting dose.

The mean survival of all trilostane treated dogs was 661 days. Direct comparison with mitotane was difficult as 65% of the dogs were still alive at the time of censor and therefore the mean survival may still increase. By comparison, the mean survival of mitotane treated dogs has been reported to be 810 to 900 days.

**Dosage and administration**

The current suggested initial starting dose range for dogs with PDH is 1-2 mg/kg once daily. This needs to be adjusted according to clinical signs and serum cortisol values (see below). Doses up to 40-50 mg/kg (divided twice daily) have been given with no unwanted side effects. In some dogs twice daily dosing may be necessary. The drug is given with food.

**Transsphenoidal hypophysectomy**

A variety of treatments are available for PDH. Medical treatment options include drugs that chemically destroy the adrenals (lysodren or op-DDD) inhibit enzymes in the adrenal leading to the synthesis of cortisol (ketoconazole, trilostane) or inhibit the release of ACTH from the pituitary gland (Anipryl or selegiline). While these treatments can improve the clinical signs in 40-80% of patients they need to be chronically administered, necessitate frequent monitoring and do not cure or address the primary cause of the disease (the pituitary tumor). In humans, surgery to remove the tumor is the most successful long-term therapy. The most common approach used is the transsphenoidal method, in which a passage way is made in the sphenoid sinus, an air space behind the back of the nose, which is just below the pituitary gland. Surgical cure rates for PDH are reported to be in the range of 65-85%, although more recent long-term follow up data suggest that the recurrence rate is as high as 25% within 5 years. When no discrete adenoma can be identified, remission of hypercortisolism is observed in only about 40%. Surgery has also been used to treat PDH in dogs. Several groups, most notably in the Netherlands have performed these surgeries with success rates paralleling those reported for humans. However, these surgeries have generally not been performed in the US. Veterinarians at VCAWLAAH, in collaboration with human neurosurgeons that regularly perform transsphenoidal surgery in humans have developed the methods to perform these surgeries in the US and are conducting a research study to determine how effectively these surgeries can be performed.
Feline acromegaly is a disease characterized by excessive growth hormone secretion. Growth hormone is produced in the pars distalis of the anterior pituitary, specifically by acidophilic cells called somatotrophs. The release of growth hormone is regulated by many factors, the most important being growth hormone releasing hormone (GHRH) produced in the hypothalamus. Recently, another hormone called ghrelin has been identified as also being a potent stimulator of the release of growth hormone. Ghrelin is released by the stomach after it has received a meal. Release of growth hormone is inhibited by the hypothalamic hormone somatostatin. In addition growth hormone itself and insulin like growth factor-1 (IGF-1) exhibit negative feedback on the release of growth hormone.

Feline acromegaly is caused by a functional adenoma of the pituitary that releases growth hormone despite negative feedback, which leads to excessive growth hormone production and release. Growth hormone has 2 classes of actions. The first are the catabolic actions of growth hormone that includes insulin antagonism, lipolysis, and gluconeogenesis with the end effect of creating hyperglycemia. The second class of actions are the slow anabolic (or hypertrophic) effects. These effects are mediated by insulin like growth factors which are produced in many different tissues. The most important is insulin like growth factor-1 (IGF-1) which is produced in the liver. The net effects of the anabolic actions of growth hormone are responsible for the characteristic appearance of acromegalic people, dogs and cats.

Feline acromegaly is an uncommon disease although it may be under diagnosed. A recent study in the United Kingdom measured IGF-1 levels in variably controlled diabetic cats. Of the 184 cases, 59 (32%) had markedly increased IGF-1 concentrations. Eighteen of these 59 cats underwent pituitary imaging and confirming a diagnosis of acromegaly in 17/18 (94%).

**Signalment, history, clinical signs**

Feline acromegaly most commonly affects middle aged to older, male castrated cats. In the aforementioned study 15 of the 17 cats diagnosed with acromegaly were males with an average age of 10.1 years. This association may be biased, however, as most cats that are diagnosed with acromegaly present for insulin resistant diabetes mellitus which is also most common in older, male castrated cats. Based on available data there is no known breed association for acromegaly.

Most acromegals present for insulin resistant diabetes mellitus (insulin doses greater than 1.5-2.2 units/kg BID) with concurrent weight gain rather than weight loss. Growth hormone theoretically affects all the tissues of the body and therefore the disease has a range of clinical signs. Physical characteristics of acromegaly include increased body weight, broadened face, enlarged feet, protrusion of the mandible (prognathia inferior), increased interdental spacing, stertorous breathing, organomegaly, and poor haircoat. Cardiovascular signs include the presence of a heart murmur, hypertension, arrhythmias (gallop), and is associated with hypertrophic cardiomyopathy. Neurologic disease associated with feline acromegaly is uncommon but can occur with a pituitary macroadenoma. Neurologic signs that have been observed with acromegaly include dullness, lethargy, abnormal behavior, circling, and blindness. Glomerulopathy and secondary renal failure has also been associated with feline acromegaly. Histopathologic evaluation of the kidneys from acromegalic cats have revealed thickening of the glomerular basement membrane and Bowman’s capsule, periglomerular fibrosis, and degeneration of the renal tubules. Arthropathy and peripheral (diabetic) neuropathy have been shown to cause lameness in acromegalic cats.

**Diagnosis**

Diagnosis of feline acromegaly starts with clinical suspicion, using a thorough history, signalment and clinical signs. Minimum database abnormalities include erythrocytosis, hyperglycemia, increased liver enzymes (ALT, ALP), hypercholesterolemia, hyperphosphatemia, hyperglobulinemia, and azotemia. Common findings on urinalysis include glucosuria, ketonuria, proteinuria, and isosthenuria. Many of these abnormalities reflect concurrent diabetes mellitus.

Specific assays for feline growth hormone are not widely available. An ovine test for feline growth hormone has been validated for use, but is only available in Europe. However, growth hormone concentration may not be a reliable diagnostic on its own. Growth hormone production is cyclic and levels may vary throughout the day. A single low or high value may not necessarily be diagnostic for acromegaly. Additionally, it has been shown that growth hormone may be elevated in non-acromegalic diabetic cats. This is due to the fact that portal insulin is required for the liver to produce IGF-1. In diabetics that are being treated with insulin subcutaneously, portal insulin concentrations remain low resulting in decreased IGF-1 production and decreased inhibition of GH release. Growth hormone levels may also not be elevated early in the course of the disease, but later typically increase significantly.

IGF-1 is the most commonly used endocrine assay used to diagnose feline acromegaly and it is widely available through the Michigan State University Diagnostic Center for Population and Animal Health. Unlike growth hormone, IGF-1 concentrations are less likely to fluctuate over the course of the day as the majority of IGF-1 is protein bound giving it a longer serum half-life. Insulin like growth factor-1 increases in response to chronically elevated growth hormone concentrations and is thought to be a reflection of...
growth hormone levels over the last 24 hours. However, just like growth hormone, elevations in IGF-1 concentration alone may not be diagnostic for acromegaly. One study found that IGF-1 levels in non-acromegalic cats on long-term insulin treatment (>14 months) had higher levels of IGF-1 than non-diabetics. The proposed mechanism for this was that insulin treatment allowed for beta cell regeneration and increased portal insulin leading to elevations in IGF-1. A subsequent study evaluating IGF-1 levels in confirmed acromegalic diabetics, non-acromegalic diabetics, and healthy cats found that acromegalic diabetics had significantly higher levels of IGF-1 than diabetics and non-diabetics. This study concluded that IGF-1 was 84% sensitive and 92% specific for diagnosing feline acromegaly. No correlation between long-term insulin use and elevations in IGF-1 concentrations were found in this study.

**Diagnostic imaging**
Radiographic findings associated with feline acromegaly are related to the hypertrophic effects of excessive growth hormone. Hyperostosis of the calvarium, spondylosis of the spine, and protrusion of the mandible are common findings. Periosteal reaction, osteophyte production, soft tissue swelling, and collapse of joint spaces are signs associated with the degenerative joint arthropathy linked to feline acromegaly. Thoracic radiographs may reveal cardiomegaly (hypertrophic cardiomyopathy) or congestive heart failure. Non-specific signs such as abdominal organomegaly (hepatic, renal, and adrenal) may be revealed by abdominal ultrasound.

Advanced imaging is needed to document the presence of a pituitary macroadenoma. Computed tomography (CT) and magnetic resonance imaging (MRI) are both useful for identifying pituitary masses. However one study found MRI to be the more sensitive imaging modality. The presence of a pituitary tumor alone is not diagnostic for feline acromegaly as there are other tumor types that can affect the pituitary. Conversely, the absence of a pituitary mass does not rule out acromegaly as there have been reported cases where a patient had a negative MRI but a pituitary mass was identified at necropsy and histopathology confirmed a growth hormone secreting adenoma.

**Histopathology**
Histopathology is needed for definitive diagnosis which makes ante-mortem diagnosis challenging. However, with advancements in surgical procedures such as transsphenoidal hypophysectomy, surgical excisional biopsy is possible. Histopathology of pituitary tumors in acromegalic cats reveals acidophil proliferation and adenoma formation.

**Adrenocortical testing**
There is no single test for the diagnosis of feline acromegaly. Clinical suspicion based on a thorough history and physical exam are essential. As earlier stated the most common presenting complaint for patients with acromegaly is insulin resistance. The 2 most common causes of insulin resistance in cats are hyperadrenocorticism and acromegaly. Both of these diseases can be associated with a pituitary mass and bilateral adrenomegaly. As such, all suspected acromegalics should undergo adrenocortical function testing via the ACTH stimulation test and/or low dose dexamethasone suppression test. Normal results on these tests would then be an indication to screen for acromegaly.

**Medical management**
Somatostatin is a hypothalamic hormone that acts on the pituitary to inhibit growth hormone release. Somatostatin analogs are commonly used in human medicine for the treatment of acromegaly and have efficacy rates approaching 90%. The somatostatin analog, octreotide, has been evaluated in a small number of feline acromegalics with limited success. One study in 4 cats, found no change in growth hormone concentrations following treatment. Another study measured the short term effects of octreotide in 5 feline acromegalics and found a decrease in growth hormone concentrations for up to 90 minutes. The results of the second study warrant further examination of somatostatin analogs especially newer long-acting formulations (name them here). Future studies are also required to identify the somatostatin receptor subtypes being expressed on feline pituitary adenomas and determine if these receptor subtypes are similar to the ones found in humans.

Growth hormone receptor antagonists and dopamine agonists are also used in human medicine. I would briefly mention the efficacy of these medications in humans. The use of growth hormone receptor antagonists has not been reported in cats. A single case study using a dopamine agonist (L-deprenyl) for the treatment of feline acromegaly showed no effect on reducing insulin requirements or clinical signs of disease.

Finally increasing the dosage of insulin to gain control of the clinical signs of the diabetes, is the most conservative choice for treating insulin resistant diabetics with acromegaly. However, there have been reports that some of these patients suddenly and inexplicably become sensitized to insulin resulting in hypoglycemic crises. In one study, several acromegalic cats were euthanized after experiencing severe episodes of hypoglycemia.

**Surgical treatment**
Surgical removal of the pituitary tumor (adenectomy) is the treatment of choice for acromegaly in human medicine. The procedure can be performed in cats and dogs as well usually employing complete removal of the entire pituitary (hypophysectomy). Availability
is limited and the only hospital that regularly performs the procedure in the United States is the VCA West Los Angeles Animal Hospital, though other institutions may soon be able to offer this option. In veterinary medicine a transsphenoidal approach is used involving only a small incision through the soft palate and then approaching the pituitary gland through the basisphenoid bone. Complications associated with the surgery include, hemorrhage, incision dehiscence and formation of an oronasal fistula. Additionally, after surgery the patient’s are at risk for hypopituitarism and may require life long supplementation with cortisone, l-thyroxine, and desmopressin making patient selection an important pre-requisite for surgery. The same surgical procedure is also used to treat pituitary dependant hyperadrenocorticism. A study in which 7 cats with pituitary dependant hyperadrenocorticism were treated with transsphenoidal hypophysectomy resulted in 5 cats showing complete resolution of the disease. Four of these cats had concurrent diabetes mellitus, 2 of which showed increased insulin responsiveness after surgery. A single case report exists for the treatment of feline acromegaly with transsphenoidal hypophysectomy. Prior to surgery the patient was also an insulin resistant diabetic that was still clinical despite receiving 25 U of insulin 4 times per day. Three weeks after surgery the patient no longer required any insulin therapy and up to a year later the patient’s IGF-1 and GH concentrations were within normal limits (no further follow up was available in the study).

We can put in our cat that underwent surgery here. Do you have the images of the MRI?

An alternative procedure, cryohypophysectomy, has been reported in 2 cats but the procedure has shown to be less effective and resulted in increased complications.

**Radiation**
Radiation therapy is another option for the treatment feline acromegaly especially if the tumor is inoperable, the patient is not a suitable candidate for anesthesia, or if surgical treatment is not available. In human medicine radiation therapy is regarded as a second line treatment due to undesired long-term effects of radiation on brain tissue. However, in veterinary medicine many of our patients, especially those that suffer from acromegaly, are not expected to live long enough to experience these long-term side effects. The majority of studies that have been performed in veterinary medicine focus on the treatment of pituitary tumors in general regardless of underlying etiology for the sake of sample size. There is no standard treatment protocol for pituitary masses in veterinary medicine and varying methods have been used including both single and multiple dose fractions administering total dosages ranging from 1,500 – 4,500 cGY. The majority of the cats included in these studies had insulin resistant diabetes (suspected acromegaly or Cushing’s disease) and/or neurologic signs. Response to treatment was good as most patients responded (Can you list % of cats having remission of clinical signs, remission of diabetes and overall survival for a few of these studies?) . Neurologic improvement was seen within weeks to months and an improved insulin response was seen within the first month, however, most still required insulin therapy. In cases where repeat imaging was available a decrease in tumor size was also noted. Disadvantages of radiation therapy are the early and delayed effects of radiation, repeated anesthesia, and expense. Early effects from radiation therapy include hair loss, skin pigmentation and otitis externa. Reported late side effects include brain tissue necrosis, tumor regrowth, and visual and hearing impairment.

**Conclusion**
Feline acromegaly is likely an under diagnosed disease in older male cats, especially in patients with insulin-resistant diabetics. There is no single diagnostic test for acromegaly. The diagnostician should use history, clinical signs, laboratory tests (GH and IGF-1), and advanced imaging to arrive at a diagnosis. There are several treatments options, however, clinical studies on long-term safety and efficacy are limited and often lack controls. Until more work is done evaluating medical treatments such as somatostatin analogues and growth hormone antagonists, most patients are best treated with either surgery or radiation therapy to control GH levels, improve glycemic control, and either remove or control the growth of the pituitary tumor.
Hyperadrenocorticism

Hyperadrenocorticism develops most commonly in middle-aged to older cats (mean age = 10.4 years; range 6 - 15 years). Of the reported cases of feline Cushing’s syndrome (78%) have been females. This female sex predilection resembles the human syndrome and contrasts with canine hyperadrenocorticism, where no sex predilection occurs.

The most common historical findings and clinical signs associated with feline hyperadrenocorticism are polyuria, polydipsia, and polyphagia. These signs likely correspond to the high incidence of concurrent diabetes mellitus (76%) found in cats with hyperadrenocorticism, and are consistent with the lack of overt signs preceding marked glucose intolerance observed in experimentally-induced disease. The typical “Cushingoid” pot-bellied appearance with hepatomegaly, weight gain, and generalized muscle wasting is common in cats as in dogs. Dermatologic abnormalities frequently recognized include an unkempt hair coat with patchy alopecia, and very thin skin prone to traumatically induced tears and secondary infections.

Hyperglycemia is the most common laboratory abnormality found on serum biochemistries. Cats appear more sensitive to the diabetogenic effects of glucocorticoid excess than dogs. Cats with concurrent diabetes mellitus often exhibit cortisol-induced insulin resistance, requiring high daily doses of insulin to control their hyperglycemia and glucosuria. Hypercholesterolemia is also common, and may relate to insulin resistance and increased lipolysis. Cats lack the steroid-induced isoenzyme of alkaline phosphatase found in the canine, and the half-life of the enzyme appears to be significantly shorter in the cat. Elevation of serum alkaline phosphatase (SAP) is present in only approximately one-third of cats compared to nearly 90% of dogs with hyperadrenocorticism. Increases in SAP and the hepatocellular enzyme ALT appear to correspond with the regulation of the diabetic state, rather than representing direct indicators of glucocorticoid excess. These enzymes frequently normalize with adequate regulation of diabetes, even without therapy directed towards the hyperadrenocorticism. Hematologic findings associated with hypercortisolism (lymphopenia, eosinopenia, and neutrophilic leukocytosis) occur inconsistently in feline hyperadrenocorticism. Despite clinical polyuria and polydipsia, cats appear to maintain urine specific gravities of greater than 1.020 more frequently than dogs, and only occasionally exhibit dilute urine and decreased blood urea nitrogen concentrations commonly seen in dogs with hyperadrenocorticism.

Endocrinologic evaluation of cats suspected of hyperadrenocorticism involves screening tests to confirm the diagnosis, and differentiating tests to distinguish pituitary-dependent disease (PDH) from adrenal tumors (AT). Adrenocorticotropin (ACTH) stimulation testing in adrenocortical hyperfunction is not as definitive as for hypoadrenocorticism. Fifteen to 30% of cats with confirmed hyperadrenocorticism have had normal cortisol response to ACTH administration (false negatives). In addition, stressed cats and those with non-adrenal illnesses may show an exaggerated response to ACTH in the absence of hyperadrenocorticism (false positives). A normal urine cortisol-to-creatinine ratio (UCCR) can be used to exclude the diagnosis of hyperadrenocorticism in cats as described in dogs. The UCCR is attractive due to the ease of sampling compared to other endocrine function tests, but is non-specific and will be elevated in a variety on non-adrenal illnesses. An exaggerated ACTH stimulation test or an elevated UCCR should be pursued with suppression testing prior to initiating any therapy.

Normal cats are more variable than dogs with respect to the degree and duration of adrenocortical suppression following dexamethasone administration. Intravenous doses of dexamethasone that have been evaluated in the cat range from 0.005 to 1.0 milligrams per kilogram. A dosage of 0.01 mg/kg of dexamethasone, commonly used in low-dose dexamethasone suppression testing in dogs, led to a significant drop in serum cortisol levels in ten normal cats, but 2 of the cats showed a slight escape from suppression by 8 hours after injection. Intravenous dexamethasone sodium phosphate (DSP), 0.01 and 0.1 mg/kg, produced equivalent reductions of plasma cortisol levels, but suppression was sustained below baseline longer with the higher dosage. Cats with various non-adrenal illnesses have also shown inadequate cortisol suppression after a low-dose (0.01 mg/kg) of DSP. The 0.1 mg/kg dosage of dexamethasone seems to more reliably suppress cortisol levels in normal cats and cats with non-adrenal illnesses. Elevated cortisol levels eight hours post-dexamethasone injection, using the 0.1 mg/kg dosage, appears to be a sensitive a diagnostic test for feline hyperadrenocorticism (89%) similar to the low-dose (0.01 mg/kg) screening test in the dog.

The combined dexamethasone suppression/ACTH stimulation test has been used successfully to diagnose hyperadrenocorticism in the cat. Affected cats display inadequate suppression of cortisol 2-4 hours after an injection of 0.1 mg/kg of dexamethasone, and an exaggerated response 1-2 hours after ACTH stimulation. The ability of the combined test to discriminate PDH from AT is unclear. Several cats with confirmed pituitary disease failed to suppress 2-4 hours after dexamethasone. Extending the duration of post-dexamethasone monitoring, or using higher doses of DSP may improve the ability of the combined test to distinguish PDH from AT. Currently, the combined test does not appear to offer more clinical utility than either the ACTH stimulation or dexamethasone suppression test evaluated separately.
An ultra-high dose, 1.0 mg/kg, dexamethasone suppression test has been used to distinguish PDH from AT in the cat. Two cats with hyperadrenocorticism diagnosed by the combined high dose dexamethasone suppression/ACTH stimulation test had exaggerated responses to ACTH with no cortisol suppression 2-4 hours after 0.1 mg/kg DSP. These cats did suppress following the ultra-high dose of dexamethasone, and were later confirmed to have PDH. Cortisol levels should be monitored at several time points following dexamethasone administration to determine if any suppression (a 50% or greater reduction in pre-test values) is occurring. Cats with PDH may show suppression 2, 4, or 6 hours into the test only to escape from the suppressive effects of dexamethasone by 8 hours. One cat with an adrenal adenoma failed to suppress following dexamethasone doses ranging from 0.1 to 1.0 mg/kg. As is the case in dogs, suppression following high doses of dexamethasone is diagnostic for PDH, but failure to suppress requires further testing to distinguish pituitary from adrenal disease.

Determination of plasma ACTH concentrations is an effective way of diagnosing PDH. The normal range of plasma ACTH is lower in cats than in dogs, and many normal cats may have concentrations of ACTH below the lower limits of the sensitivity of the assay. Cats with PDH will have normal to elevated ACTH concentrations while cats with adrenocortical adenomas or carcinomas will have undetectable plasma ACTH levels. Plasma ACTH samples need to be collected and handled carefully. Veterinarians should consult their diagnostic laboratory for specific instructions prior to performing the test. Incorrect sample handling can falsely lower measured values. Normal to elevated plasma ACTH levels support a diagnosis of PDH, whereas low concentrations may require additional diagnostic testing. As in the differentiation of canine hyperadrenocorticism, ACTH levels should only be used to distinguish PDH from AT after hyperadrenocorticism has been confirmed by other screening diagnostics.

Pituitary-adrenal function tests need to be interpreted in conjunction with historical, clinical, and clinicopathologic findings before any conclusions can be drawn. No single diagnostic test is infallible. Equivocal results or discordant findings should be reevaluated. Hyperadrenocorticism is an uncommon disorder in cats. Consequently, false positive test results should be anticipated. Interpretation of endocrinologic testing should incorporate all available information before any therapeutic intervention is attempted.

Diagnostic imaging can facilitate differentiation of PDH from AT when screening tests and clinical findings suggest hyperadrenocorticism. Approximately half of canine adrenal tumors are mineralized and can be recognized radiographically. The frequency of mineralization in feline adrenocortical tumors is unknown, but up to 30% of normal cats may have calcification of their adrenal glands. Abdominal radiographic findings in cats with hyperadrenocorticism included hepatomegaly (69%) and obesity. Ultrasonographic evaluation of adrenal size and morphology has been described for dogs and cats. Nonfunctional adrenal tumors can be incidental findings in humans undergoing abdominal imaging. The incidence of "silent" adrenal masses in the cat is unknown. The presence of unilateral adrenomegaly or distortion of adrenal architecture in a cat suspected of hyperadrenocorticism is strong evidence of AT. Abdominal computerized tomography (CT) and magnetic resonance imaging (MRI) offer improved resolution for the detection of adrenal tumors or hyperplasia. CT and MRI detection of pituitary masses is also now feasible for small animal patients.

Adrenal tumors accounted for 22% of the reported cases of feline hyperadrenocorticism. Half of the adrenocortical tumors were found histologically to be adenomas and half carcinomas. The treatment of choice for adrenal tumors is surgical adrenalectomy. Two cats with adrenocortical adenomas responded well to unilateral adrenalectomy, with clinical signs resolving over 4 to 8 weeks. One cat with an adrenal adenoma removed surgically developed a recurrence of signs 12 months postoperatively. An adenoma of the contralateral adrenal gland was diagnosed. The cat survived a second adrenalectomy and was disease-free for over two years following the second procedure. Surgical therapy and long term follow-up for adrenocortical carcinomas in cats has not been reported.

Treatment options for pituitary dependent hyperadrenocorticism in the cat include both surgical and medical alternatives. Bilateral adrenalectomy followed by mineralocorticoid and glucocorticoid replacement therapy was performed in 11 cats. Nine cats responded well to surgery with cessation of polyuria and polydipsia, regrowth of hair coat, and marked improvement (4) or resolution (5) of diabetes mellitus. One cat developed acute signs of circling, wandering aimlessly, and apparent blindness 2 months post-operatively. An expanding pituitary tumor was suspected, but no necropsy was performed. Two cats died within one week of surgery from sepsis. Survival times for 6 cats with adequate follow-up after bilateral adrenalectomy for PDH ranged from 1 to 12+ months (median 5 months). Two cats are still alive, one year post-operatively. These results suggest that surgical complications of bilateral adrenalectomy may be less frequent in cats than in dogs.

Surgical treatment can also include transeptal hypophysectomy which is performed at WLA for cats with pituitary masses extending above the sella (macroadenoma). Cats with functional tumors have similar success rates to those reported in dogs with PDH.

Four drugs (ketoconazole, mitotane, metyrapone and trilostane) have been investigated for the medical management of spontaneous feline hyperadrenocorticism. Ketoconazole, an antifungal imidazole derivative, has been shown to inhibit adrenal and gonadal steroidogenesis in humans and dogs. One month of ketoconazole (15mg/kg orally twice daily) administration in 4 cats did not significantly reduce baseline plasma cortisol or ACTH responsiveness at doses 3 times greater than those effective in dogs. Two of 4 cats treated with 10 - 20 mg/kg/day of ketoconazole had adequate control of hypercortisolemia. One of the 4 cats developed severe thrombocytopenia after only one week of therapy and had to discontinue the medication. A cat with adrenocortical adenocarcinoma
treated with 30 mg/kg/day for 3½ months showed improved regulation of diabetes and reduction in pu/pd despite no improvement in hyperresponsiveness to ACTH. The cat ultimately was euthanatized subsequent to a non-healing skin laceration, chronic infections, and worsening insulin resistance. No evidence of hepatotoxicity or thrombocytopenia was seen at the 30 mg/kg/day dosage of ketoconazole, but the effectiveness and safety of this therapy remains questionable.

Mitotane, o,p'-DDD, is an adrenal cytotoxic agent and has been used successfully to treat dogs with PDH and AT. Use of mitotane in cats has been discouraged due to the feline sensitivity to chlorinated hydrocarbons. Three of 4 normal cats treated with o,p'-DDD at dosages ranging from 25 - 50 mg/kg, divided twice a day, tolerated the drug well, and remained clinically normal throughout treatment with mitotane. Only 2 of the 4 cats showed a decreased responsiveness to ACTH with mitotane. The cat with the largest reduction in post-ACTH cortisol levels developed vomiting, diarrhea, and partial anorexia lasting 2 weeks after a 50 mg/kg dosage of mitotane. Two cats with PDH treated with o,p'-DDD (25 mg/kg/day x 25 days, and 25 - 50 mg/kg/day x 59 days) tolerated the drug without apparent toxicity, but therapy was ineffective in controlling clinical signs in either cat. A cat with PDH treated with mitotane (50 mg/kg/day x 1 week, then 50 mg/kg/week) developed signs compatible with iatrogenic hypoadrenocorticism after 40 weeks of therapy with o,p'-DDD. At that time the cat was anorectic, lethargic, and exhibiting neurologic signs including mydriasis, pacing, and head pressing. Computerized tomography revealed a large pituitary mass extending above the sella turcica. Mitotane was discontinued, and the cat was treated with 60Co teletherapy. Subsequent CT examinations revealed shrinkage and then disappearance of the mass 10 months post-irradiation. The cat was euthanatized for continued diabetes mellitus and post-irradiation cataracts 2 years after the initial diagnosis of hyperadrenocorticism. We have had 3 other cases where a positive response to mitotane was observed clinically.

Metyrapone, an inhibitor of the 11-b-hydroxylase enzyme that converts 11-deoxycortisol to cortisol, has been used effectively in man to reduce the clinical signs of hypercortisolemia. A reciprocal rise in plasma ACTH levels occurs with falling cortisol concentrations and can eventually override the enzymatic block, allowing a return of clinical signs. In humans, metyrapone is utilized as an adjunctive therapy with pituitary irradiation or surgery. Dosages ranging from 195 - 250 mg/day have been used in cats with hyperadrenocorticism without observed toxicity. In a recent report, a diabetic cat with PDH and severe nonhealing skin wounds was treated with 65 mg of metyrapone orally 3 times a day. After 2 days of therapy the cat developed signs of glucocorticoid deficiency including depression, tremors, and ataxia. The cat improved rapidly following treatment with injectable steroids, and was discharged on twice daily metyrapone therapy. Cortisol response to exogenous ACTH was absent when evaluated on day 7. The cat was re-examined 24 days later after a hypoglycemic episode. The cats skin wounds had resolved and hair regrowth was evident. A follow-up ACTH stimulation test revealed a slightly exaggerated response. The cat underwent successful bilateral adrenalectomy and was euglycemic, with a normal haircoat, 4 months post-operatively. Two of 3 other cats reported in the literature also showed clinical improvement with metyrapone therapy, but follow-up periods were short (less than 6 months). Whether longterm therapy with metyrapone can control hypercortisolemia in cats, or whether rising ACTH levels eventually overwhelm enzymatic blockade has not been determined. Metyrapone appears to permit rapid correction of hyperadrenocorticism in some cats, and may be useful for presurgical stabilization prior to adrenalectomy.

We have recently evaluated the safety and efficacy of trilostane therapy (Vetoryl, Dechra Pharmaceuticals) in 15 cats with PDH. Clinical signs (13 of 15 cats) and ACTH stimulation testing results (13 of 15) improved with trilostane therapy. Diabetes mellitus was reported in 9/15 cases. Insulin requirements decreased by 36% within 2 months in 6/9 diabetic cats. Median survival time was 617 days for all cats (range 80-1,278 days). Complications included weight loss, urinary tract infections, chronic kidney disease, seizures, and recurrent pancreatitis. Hypocortisolemia was documented in 1 case. Cause of death occurred as a result of non-adrenal or non-diabetic illnesses (renal failure, seizures [caused by hypoglycemia or unknown]), or lymphoma. Trilostane ameliorates clinical signs of HAC in cats, is tolerated well in the long term, and can lead to improved regulation of diabetes. It should be considered first line therapy for cats undergoing medical management of PDH.

Hypoadrenocorticism
Primary hypoadrenocorticism has been described in cats. Addisonian cats are middle-aged, with a median age of 4 years (mean 5.8 +/- 3.7 years) and range in age from 1.5 to 14 years. No sex or breed predilection is seen. The most common historical problems include lethargy, anorexia, and weight loss. Unlike dogs with adrenal insufficiency, diarrhea is not noted in Addisonian cats. Forty percent of cats have histories of episodic vomiting. Similar to hypoadrenocorticism in the canine, cats often have a waxing and waning clinical course, including temporary "remissions" associated with parenteral fluid and/or corticosteroid administration.

The most common findings on physical examination include depression, weakness, and mild to severe dehydration. Up to 40% present with in severe shock with weak pulses, slow capillary refill times, and extreme weakness or collapse. The duration of clinical signs preceding the diagnosis of hypoadrenocorticism ranges from 5 to 100 days, with a median of 14 days. Clinicopathologic findings in cats with primary hypoadrenocorticism parallel the patterns seen in the dog. Serum electrolyte changes characteristic of mineralocorticoid deficiency are seen in most cats. Serum sodium:potassium ratios are less than 24 (range
17.9-23.7) with hyponatremia, hypochloremia, and hyperkalemia. All cats have had mild to severe azotemia (blood urea nitrogen 31-80 mg/dl, normal range 5-30 mg/dl; creatinine 1.6-6.0 mg/dl, normal range 0.5-1.5 mg/dl), and hyperphosphatemia (inorganic phosphorus 6.1-9.1 mg/dl; normal range 3.0-6.0 mg/dl). Hypercalcemia has been noted in one cat. Despite signs of dehydration and preeclampsia, urine specific gravity was greater than 1.030 in only 40% of cats. The loss of renal medullary solutes, particularly sodium, is believed to result in impaired renal concentrating ability. Distinguishing hypoadrenocorticism from acute or chronic renal failure is critical to establishing an appropriate prognosis for clients.

Long-term management of cats with primary hypoadrenocorticism requires lifetime mineralocorticoid and glucocorticoid supplementation. Oral fludrocortisone acetate (0.1 mg/day) or intramuscular injections of desoxycorticosterone pivalate (DOCP; 10 - 12.5 mg/month) have been successful in maintaining Addisonian cats. The dose of mineralocorticoid is adjusted as needed based on follow-up serum electrolyte concentrations monitored every one to two weeks during the initial maintenance period. Normal electrolyte parameters 2 weeks following DOCP suggests adequate dosing, but does not provide information concerning the duration of action of each injection. Eighty percent of dogs require DOCP more frequently than every 30 days (5% need to receive DOCP every 3 weeks), so frequent sampling during the early management period is recommended. Prednisone, 1.25 mg orally once a day, or intramuscular methylprednisolone acetate, 10 mg once a month, can be used to provide adequate long term glucocorticoid supplementation. Cats surviving the initial adrenal crisis can be managed successfully for many years. 60% of cats diagnosed with primary hypoadrenocorticism are alive a median of 2.75 years after diagnosis. With appropriate glucocorticoid and mineralocorticoid supplementation, cats with adrenocortical insufficiency should have a normal life expectancy.

**Primary hyperaldosteronism**

Feline primary hyperaldosteronism is diagnosed based on clinical signs, serum biochemistry, plasma aldosterone concentration, adrenal imaging and histopathology of adrenal tissue. Cats may present with blindness caused by systemic hypertension. Many will also present with weakness resulting from hypokalaemic polymyopathy. Elevated concentrations of plasma aldosterone and adrenocortical neoplasia have been documented in all cases. Seven cases had adrenal adenomas (unilateral in five and bilateral in two) and six had unilateral adrenal carcinomas. Three cases underwent medical treatment only with amlodipine, spironolactone and potassium gluconate; two cases survived for 304 and 984 days until they were euthanized because of chronic renal failure, while the third case was euthanized at 50 days following failure of the owner to medicate the cat. Ten cases underwent surgical adrenalectomy following a successful stabilization period on medical management. Five cases remain alive at the time of writing with follow-up periods of between 240 and 1803 days. Three cases were euthanized during or immediately following surgery because of surgical-induced hemorrhage. One cat was euthanized 14 days after surgery because of generalized sepsis, whilst the remaining cat was euthanized 1045 days after surgery because of anorexia and the development of a cranial abdominal mass. It is recommended that primary hyperaldosteronism should be considered as a differential diagnosis in middle-aged and older cats with hypokalaemic polymyopathy and/or systemic hypertension and this disease should no longer be considered a rare condition.

In recent years, there has been renewed interest in primary hyperaldosteronism, particularly because of its possible role in the progression of kidney disease. While most studies have concerned humans and experimental animal models, a recent paper highlighted the occurrence of a spontaneous form of (non-tumorous) primary hyperaldosteronism in cats. At presentation, the main physical features of 11 elderly cats were hypokalaemic paroxysmal flaccid paresis and loss of vision due to retinal detachment with hemorrhages. Primary hyperaldosteronism was diagnosed on the basis of plasma concentrations of aldosterone (PAC) and plasma rennin activity (PRA), and the calculation of the PAC:PRA ratio. In all animals, PACs were at the upper end or higher than the reference range. The PRAs were at the lower end of the reference range, and the PAC:PRA ratios exceeded the reference range. Diagnostic imaging by ultrasonography and computed tomography revealed no or only very minor changes in the adrenals compatible with nodular hyperplasia. Adrenal gland histopathology revealed extensive micronodular hyperplasia extending from zona glomerulosa into the zona fasciculata and reticularis. In three cats, plasma urea and creatinine concentrations were normal when hyperaldosteronism was diagnosed but thereafter increased to above the upper limit of the respective reference range. In the other eight cats, urea and creatinine concentrations were raised at first examination and gradually further increased. Even in end-stage renal insufficiency, there was a tendency to hypophosphatemia rather than to hyperphosphatemia. The histopathological changes in the kidneys mimicked those of humans with hyperaldosteronism: hyaline arteriolar sclerosis, glomerular sclerosis, tubular atrophy and interstitial fibrosis. The non-tumorous form of primary hyperaldosteronism in cats has many similarities with "idiopathic" primary hyperaldosteronism in humans. The condition is associated with progressive renal disease, which may in part be due to the often incompletely suppressed plasma renin activity.

**References**
