The Sometimes Tricky Art of Diagnosing Hyperadrenocorticism in Dogs

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1. Introduction
   A. Cushing's syndrome refers to all causes of hyperadrenocorticism with overproduction of cortisol.
      a. ACTH-dependent
         i. Cushing's disease: Pituitary hypersecretion of ACTH which results in bilateral adrenal hyperplasia
            (90% of cases)
         ii. Ectopic ACTH production: Non-pituitary tumors secreting ACTH resulting in bilateral adrenal
             hyperplasia. Has not been completely documented in dogs or cats.
      b. ACTH independent
         i. Adrenocortical adenoma or carcinoma: Hypersecretion of cortisol with atrophy of normal adrenal
            and suppressed ACTH concentrations (10% of cases).
      c. Iatrogenic
         i. Excessive or prolonged administration of glucocorticoids. Clinically indistinguishable from natural
            disease. Results in adrenal atrophy and suppressed ACTH levels.

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

3. Clinical signs
   A. PU / PD
   B. Pendulous, "pot-bellied abdomen": Due to muscle catabolism by glucocorticoids and hepatomegaly.
   C. Bilaterally symmetric alopecia: Head and extremities spared.
   D. Thin skin
   E. Muscle weakness and muscle atrophy; cruciate ruptures
   F. Mineralization of skin (calcinosis cutis)
   G. Hyperpigmentation: ACTH similar to MSH, co-existing hypothyroidism, chronic skin irritation.
   H. Reproductive abnormalities
      a. Anestrus
      b. Clitoral hypertrophy
      c. Testicular atrophy
      d. Perianal adenomas in females and neutered males.
   I. Respiratory signs
      a. Panting: Pulmonary hypertension and decreased compliance, primary CNS disturbance, pulmonary
         mineralization.
      b. Dyspnea: Rare; seen with pulmonary thromboembolism and concurrent congestive heart failure.
   J. Central nervous system
      a. 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.
      b. Signs due to compression/invasion of pituitary and/or hypothalamus:
   K. Seizures
      a. Pacing
      b. Lethargy
      c. Inappetence
      d. Behavior change
      e. Head pressing
      f. Circling
4. Diagnosis of Hyperadrenocorticism

A. History and clinical signs
B. 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.
C. Laboratory data
   a. Hemogram
      i. Polycythemia (PCV 45-55%)
      ii. Stress leukogram
         1. Lymphopenia
         2. Eosinopenia
         3. Neutrophilia (mature)
   b. Biochemistry profile
      i. Elevations in:
         1. Serum alkaline phosphatase (SAP)
         2. Cholesterol
         3. Serum alanine aminotransferase (ALT)
         4. Fasting blood glucose: Diabetes in 5-10%.
   c. Thyroid function tests
      i. T3 and T4 basal levels are generally decreased.
      ii. Response to TSH parallels normal.
      iii. Secondary to negative feedback of cortisol on pituitary.
      iv. 80% have a normal fT4ED
      v. Does not require thyroid supplementation.
   d. Blood pressure: 50 – 80% are hypertensive, cause unknown.
      i. 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.
   e. Urinalysis
      i. Decreased urine specific gravity.
      ii. Proteinuria
D. Radiographic abnormalities
   a. Thoracic films
      i. Bronchial calcification
   b. Abdominal films
      i. Hepatomegaly
      ii. Osteopenia
      iii. 50% of adrenal tumors are visualized as soft tissue or calcified masses.
      iv. Subcutaneous calcification
E. Adrenal function tests
   a. Three tests used to diagnose hyperadrenocorticism. They do not differentiate between PDH or AT.
      i. ACTH stimulation test
         1. Look for exaggerated cortisol response in response to ACTH.
         2. See protocols at the end of this discussion.
         3. Diagnostic in 85% of pituitary-dependent cases (PDH)
         4. Diagnostic in 70% of adrenal tumors (AT)
         5. Overall accuracy 80-85 %
         6. A suppressed response to ACTH in animals with clinical signs of hyperadrenocorticism suggests iatrogenic disease.
   b. Low-dose dexamethasone suppression test
      i. Low doses of dexamethasone inhibit ACTH release from the pituitary via negative feedback and decrease plasma cortisol concentrations in normal dogs.
ii. Dogs with Cushing's are more resistant to steroid suppression. Therefore, lack of suppression following dexamethasone = hyperadrenocorticism.

iii. Diagnostic in 95% of PDH

iv. Diagnostic in 100% of AT
c. Overall 90-95%
   i. May also be used to distinguish PDH from AT (see below)
   ii. See protocols
d. Urine cortisol/creatinine ratio
   i. Assessment of cortisol production and excretion rate.
   ii. Sensitivity of this test is greater than that of the LDDS (some animals with clinical signs of hyperadrenocorticism may have normal LDDS response tests but elevated urine cortisol to creatinine ratios). Used as a screening test.
   iii. Test is easy to perform.
   iv. As with all adrenal function tests, elevated results may occur in animals with non-adrenal disease.
   v. Positive tests confirmed with a LDDS.
   vi. Must be performed on urine obtained at home, preferably in the AM
e. Tests to differentiate PDH from AT (performed after confirming diagnosis of hyperadrenocorticism).
   i. High-dose dexamethasone suppression test
      1. With PDH, a high dose of dexamethasone results in a decrease in ACTH release from the pituitary and a decrease in plasma cortisol.
      2. With AT, the tumor secretes cortisol autonomously thereby suppressing ACTH production. With low ACTH concentrations already present, dexamethasone has no effect on plasma cortisol.
      3. 70% of patients with PDH suppress plasma cortisol to less than 50% of the pre-treatment value.
      4. 100% of patients with AT do not suppress.
      5. Therefore: Suppression = PDH; Lack of suppression = Inconclusive
      6. See protocol
   f. Endogenous ACTH concentration
      i. PDH: Levels normal or high
      ii. AT: Levels low to undetectable
      iii. Contact lab regarding sample handling and collection. Use of the preservative (Aprotinin) allows for greater utilization of this test.
      iv. 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.

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

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

C. Urine Cortisol/Creaitinine Ratio
   a. First morning urine sample is preferred. Sample should be obtained at home. Requires 1 – 2 mls.
   b. Stable at room temperature or refrigerated for 3 days.

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c. Normal range 2.8 - 4.8. A normal result effectively rules-out hyperadrenocorticism, an abnormal result should be confirmed with a LDDS or ACTH stimulation test.

**Differentiating PDH From AT**

A. Low-Dose Dexamethasone Suppression Test  
   a. See above.

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

C. Endogenous ACTH Concentration  
   a. Check with lab on sample collection and handling.
   b. Normal: 20-100 pg/ml (4.4-22.0 pmol/L)
   c. PDH: 40-500 pg /ml (8.8-110 pmol/L)
   d. AT: < 20 pg/ml (<4.4 pmol/L)
Exploring Treatment Options for Canine Hyperadrenocorticism
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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.
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 levels 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 lipidosis
    - 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 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 dogs and some cats. With insulin given once a day, feed three meals a day (of equal calories) at six-hour internals. Give the first meal at the time of the insulin injection. 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.

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Re-check evaluations
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:
   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:
      - Review management with owner
      - 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:
      - Management problems
      - Hyperadrenocorticism
      - Steroid or Ovaban administration
      - Diestrus or pregnancy
      - Acromegaly
      - Concurrent illness, infection
      - Anti-insulin antibodies
      - Hypothyroidism (dogs), hyperthyroidism (cats)
   d. 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 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 unkempt 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, proptosis 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
  - Dexamathione 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)
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 thyroditis**
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 hypoechoic 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.
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.

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.
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 hyperthyroidism 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. The diagnosis of hyperthyroidism should not be excluded on the basis of a single normal serum T4 value, especially in a cat with typical clinical signs, a palpable thyroid nodule and serum T4 in the upper half of the normal 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 (Table 1). 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:

- It has the potential to eliminate a benign thyroid tumor or abnormal thyroid tissue with a single treatment
- It treats extra-thyroidal thyroid tissue, which may occur in 10 to 20% of hyperthyroid cats
- No general anesthesia is required
- 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, carbimazole) 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 carbimazole; 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 carbimazole 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 carbimazole 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 carbimazole 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.3,33-36 The presence of underlying CKD may affect the prognosis - one study documented a shorter survival time in hyperthyroid cats with azotemia.4 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.38,39

The reported occurrence of azotemia after treatment of hyperthyroidism ranges from 15 to 49%.31,35-37,40 Iatrogenic hypothyroidism has been reported to decrease GFR in human patients.41 Post-treatment iatrogenic hypothyroidism has been reported in cats after radioiodine therapy and bilateral thyroidectomy, which constituted the predominant therapeutic modalities in previous studies.40 In one recent study, cats with iatrogenic biochemical hypothyroidism were almost twice as likely to develop azotemia post-treatment as euthyroid cats.38 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.42,43 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.
Getting to the Bottom of Polyuria and Polydipsia

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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
   b. 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.
Canine Diabetes: Acute Care and Long-Term Management and Helping Clients Pay for It

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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

Canine
There are some distinct differences in the etiology of canine and feline diabetes. In dogs, it is generally thought to be an immune mediated disease with gradual destruction of beta cells. The progression from normal, to glucose intolerant, to diabetes, is generally slow so that most islets (over 90%) are lost before diabetes occurs. Other causes of diabetes in dogs include genetic predisposition, chronic pancreatitis and medication-induced diabetes (glucocorticoids and megestrol acetate).

Genetic predisposition to diabetes is most common in the following breeds: German Shepherd dogs, Schnauzers, Beagles, and Poodles. Golden Retrievers and Keeshonds are more prone to juvenile diabetes.

Gender is a factor in dogs with females being three times more likely to develop diabetes than males. Generally, diabetes occurs in dogs in middle age (6-9 years) but can also present earlier for specific breeds, particularly the Golden Retriever and Keeshond.

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 glucoses 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 lipidosis
    - 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.

**Canine patients**

**Newly diagnosed patients**

1. **Vetsulin (porcine origin lente):** A zinc, porcine, intermediate acting insulin. Canine and porcine insulin have an identical amino acid sequence thereby eliminating the theoretical complication of anti-insulin antibodies and their effect on glycemic control. The suggested, initial starting dose is 0.5 units/kg BID. This insulin is only available at a concentration of 40 iu/ml (U-40) so please make sure that proper insulin syringes are provided to the owner. Re-assessment of clinical signs and a serial blood glucose curve should be performed 1 week after starting therapy. This insulin must be thoroughly shaken before administration. For additional information see: www.vetsulin.com.

2. **Humulin N or Novolin N:** These are both intermediate acting, human origin insulins. Suggested starting doses are 0.5 units/kg BID. Re-assessment of clinical signs and a serial blood glucose curve should be performed 1 week after starting therapy. I would avoid NPH insulins from Wal Mart due to product inconsistencies.

3. **Glargine:**

4. **Detemir:**

5. **PZI:**

**Transitioning canine patients**

If you have canine patients currently taking Humulin L lente insulin, I would switch them to either Vetsulin or Humulin N. The initial dose of Vetsulin or Humulin N will remain the same with re-assessment of clinical signs and a serial blood glucose curve performed 1 week after changing insulin preparations.

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**

**Dogs**
- Dogs on NPH or Lente Insulins
  - If the preinsulin blood glucose concentration is > 360 mg/dl and/or the nadir blood glucose concentration is > 180 mg/dl the dose of insulin is increased by 25%.
  - If the preinsulin blood glucose concentration is 270 to 360 mg/dl and/or the nadir blood glucose concentration is 90 - 180 mg/dl the dose of insulin is maintained.
  - If the preinsulin blood glucose concentration is 190 - 270 mg/dl and/or the nadir 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 (50%) or maintained.
  - If the preinsulin blood glucose concentration is < 180 mg/dl and/or the nadir blood glucose concentration is < 54 mg/dl the dose of insulin is decreased by 50%.

The use of the AlphaTrak Blood Glucose Monitoring System both in the clinic and at home will greatly improve our ability to assess glycemic control and improve insulin therapy. In conjunction with close observation of clinical signs, at home glucose monitoring should go a long way towards improving the quality of life of diabetic pets and their owners.

**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 dogs and some cats. With insulin given once a day, feed three meals a day (of equal calories) at six-hour internals. Give the first meal at the time of the insulin injection. 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.

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Re-check evaluations
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
   a. Role of glycosylated hemoglobin and fructosamine:
   b. 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
- Insulin induced hyperglycemia (Somogyi phenomenon)
  o Hypoglycemia (<65mg/dl) followed by hyperglycemia (>300mg/dl) within 24 hours of insulin injection.
  o Suspect when insulin requirements exceed 2 U/kg and clinical signs persist.
  o Suspect when animal has signs of hypoglycemia in afternoon.
  o Diagnosis with serial sugars.
  o Treat by decreasing insulin dose 25-50% and review insulin administration with the owner to rule out management problems.
  o Re-check serial sugars in one week.
- Rapid insulin metabolism
  o Duration of insulin less than 18 hours.
  o Signs return in the evening.
  o Diagnosis is with serial sugars. Hyperglycemia (>250) within 18 hours of insulin injection without previous hypoglycemia.
  o Treatment:
    ▪ Review management with owner
    ▪ 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.
- Insulin Resistance
  o Hyperglycemia (>300) throughout the day, despite insulin dosages > 2 U/kg.
  o Diagnosis based on serial sugars.
  o Potential causes of insulin resistance:
    ▪ Management problems
    ▪ Hyperadrenocoticism
    ▪ Steroid or Ovaban administration
    ▪ Diestrus or pregnancy
    ▪ Acromegaly
    ▪ Concurrent illness, infection
    ▪ Anti-insulin antibodies
    ▪ Hypothyroidism (dogs), hyperthyroidism (cats)
  o If insulin dose exceeds 2U/kg, the animal should be evaluated for one of these causes of resistance.
- Hypoglycemia
  o Insulin overdosage
  o Suspect if animal shows weakness, shaking, ataxia, seizures at time of insulin's peak effect.
  o Therapy (instructions for owners)
    ▪ Mild signs - give food and call veterinarian
    ▪ Moderate signs - apply Karo syrup to the mouth, offer food when alert and then notify veterinarian.
    ▪ Comatose - apply Karo syrup to mouth and take animal to hospital.
  o When hypoglycemia occurs, serial sugars should be performed to re-assess insulin dose