Diabetes Mellitus in Dogs and Cats

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Diabetes mellitus is a common endocrine disorder in dogs and cats. Recent data has shed light on the pathogenesis of the disorder in dogs and cats and has highlighted the role of diet, insulin and novel hypoglycemic therapies. In the majority of cases, the most appropriate therapy in both dog and cats includes the administration of insulin.

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

Key Facts:

1. Insulin is still the mainstay of therapy in the majority of dogs and cats with diabetes mellitus.

2. Diet is an important part of diabetic management especially in obese patients and cats.

3. Auto-immune disease, pancreatitis and amyloidosis are the most common causes of diabetes in dogs and cats.

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

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

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

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

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

Etiology and Signalment

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
    1. non-specific
    2. signs of dehydration
- Biochemistry profile
    3. hyperglycemia
    4. increases in SAP and ALT
    5. increases in bilirubin (usually in cats)
        a) hepatic lipidosis
        b) pancreatitis
- Urinalysis
    1. glycosuria
        a) renal threshold for glucose
            canine 180-220mg/dl
            feline 240-300 mg/dl
    1. ketonuria
    2. 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 t 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 give 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, pydermas, 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 pyodermas 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 is 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.

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:
    1. Should not be diluted or mixed as this will affect pH
    2. 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 blodd 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.

Dogs

3. Dogs on NPH or Lente Insulins
    a. 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%..
    b. 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.
    c. 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.

d. 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 glyemic 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.

Re-check Evaluations

1. Obtain owner assessment of clinical signs.
2. Serial blood sugars are helpful due to:
   Variability of insulin action in a given patient.
   Inaccuracy of random blood or urine sugars in monitoring the degree of glycemic control.
   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 frustosamine:
   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)
    - Hypoglycemia (<65mg/dl) followed by hyperglycemia (>300mg/dl) within 24 hours of insulin injection.
    - Suspect when insulin requirements exceed 2 U/kg and clinical signs persist.
    - Suspect when animal has signs of hypoglycemia in afternoon.
    - Diagnosis with serial sugars.
    - Treat by decreasing insulin dose 25-50% and review insulin administration with the owner to rule out management problems.
    - Re-check serial sugars in one week.

2. Rapid insulin metabolism
    - Duration of insulin less than 18 hours.
    - Signs return in the evening.
    - Diagnosis is with serial sugars. Hyperglycemia (>250) within 18 hours of insulin injection without previous hypoglycemia.
    - 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
    - Hyperglycemia (>300) throughout the day, despite insulin dosages > 2 U/kg.
    - Diagnosis based on serial sugars.
    - 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)
    - If insulin dose exceeds 2U/kg, the animal should be evaluated for one of these causes of resistance.

4. Hypoglycemia
    - Insulin overdosage
    - Suspect if animal shows weakness, shaking, ataxia, seizures at time of insulin's peak effect.
    - 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.

- When hypoglycemia occurs, serial sugars should be performed to re-assess insulin dose