Sweet success: Managing the difficult diabetic patient

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Management of diabetes mellitus in small animals can be challenging; however, the application of a systematic method of dietary and pharmaceutical (insulin, oral hypoglycemics) interventions coupled with practical monitoring strategies can result in improved patient care and client satisfaction. This article will cover the management of newly diagnosed and complicated cases of diabetes in cats and dogs.

Feline diabetes mellitus

Diagnosis of feline diabetes mellitus
Feline diabetes is most often type 2 in nature and is one of the most common endocrinopathies of the cat. Middle-aged to older, male cats with a history of obesity are most at risk. Amylin is a hormone that is synthesized in beta cells and is co-secreted with insulin. Secretion of amylin is regulated with the secretion of insulin and both increase during insulin resistance. The incretin hormones GIP (glucose-dependent insulinotropic peptide) and GLP-1 (glucagon-like peptide-1) are secreted from the intestines in response to the presence of nutrients in the intestinal lumen. They increase the sensitivity of beta cells to glucose so that in any given concentration of glucose more insulin will be secreted. The reduction in the incretin effect in DM and prediabetes is attributed to decreased sensitivity of beta cells to the effect of GIP or a decrease in GLP-1 secretion or both. Incretin hormones also participate in regulation of beta cell differentiation, proliferation, and survival, overall contributing to increased beta cell mass. Incretin hormones also affect glucagon secretion, slow the rate of gastric emptying, and increase satiety. Cats are obligate carnivores and are therefore adapted to ultra-low carbohydrate diets. Incretin secretion is not stimulated by glucose in cats and their overall incretin effect in response to glucose is reduced. This means that a carbohydrate-rich meal will result in a relatively prolonged post-prandial hyperglycemia.

Clinical signs of type 2 diabetes mellitus are subtle and progressive over a period of months to years until blood glucose rises above the renal threshold, which is quite high in the cat, and polyuria/polydipsia ensues. Obesity combined with fasting or postprandial hyperglycemia may be the only clinical sign of early type 2 diabetes mellitus. Cats affected with diabetic neuropathy will have trouble jumping onto high surfaces such as counters and beds because the hind limbs are usually affected. As blood glucose concentrations exceed the renal threshold (which may be as high as 350 mg/dl in some cats), polyuria and secondary polydipsia become the primary clinical signs. Weight loss begins to occur as a result of insulin resistance and insulin deficiency with calories lost in glucose-laden urine.

In cats, physical examination findings of uncomplicated diabetes mellitus are typically nonspecific. The most common physical examination findings include lethargy and depression, dehydration, unkempt haircoat, hepatomegaly, and muscle wasting. Plantigrade rear limb stance resulting from diabetic neuropathy is observed in approximately 10% of diabetic cats in previous studies. In cats, signs of DM include fasting hyperglycemia, hypercholesterolemia, increased liver enzymes (ALP, ALT), proteinuria,
increased urine specific gravity, azotemia, and glycosuria. Many cats are susceptible to stress-induced hyperglycemia in which the serum glucose concentrations approach 300 to 400 mg/dL. Serum fructosamine is formed by glycosylation of serum protein such as albumin. The fructosamine concentration in serum is directly related to blood glucose concentration. However, because albumin has a shorter life span than hemoglobin has, fructosamine concentrations reflect more recent (one to three weeks) changes in serum glucose concentrations than glycosylated hemoglobin does. Measuring serum fructosamine concentrations in cats may be of benefit when trying to distinguish early or subclinical diabetes mellitus from stress-induced hyperglycemia. One study of 17 normal cats showed that transient glucose administration (1 g/kg 50% glucose solution, intravenously) did not increase serum fructosamine concentrations. In the same study, it was noted that 50% of sick cats showed mild increases in serum fructosamine concentrations consistent with subclinical to mildly clinical diabetes mellitus even when the serum glucose concentrations were in the normal or near normal range. This finding suggests that subclinical type 2 diabetes mellitus is probably much more common than previously believed and that obese cats with increased serum fructosamine levels should be followed carefully for evidence of developing diabetes mellitus. In cats, normal fructosamine concentrations are 283 ± 32 μmol/L.

Management of newly diagnosed diabetic cats
The management of newly diagnosed feline diabetic patients includes first and foremost attention to diet (Table 1). Initial studies using a canned high-protein/low-carbohydrate diet and the starch blocker acarbose have shown that 58% of cats were able to discontinue insulin injections and those with continued insulin requirements could be regulated with a much lower dosage (1 U b.i.d.). Comparison of canned high-fiber/moderate-carbohydrate diets versus low-carbohydrate/low-fiber diets showed that cats fed low-carbohydrate diets were almost twice as likely to discontinue insulin injections. Feeding newly diagnosed diabetic cats a canned low-carbohydrate, high-protein diet, such as Purina Veterinary Diets OM Dietetic Management, will result in the highest remission rates. For cats that refuse to eat canned food, Purina OM dry combined with acarbose (12.5 mg b.i.d. with food) is another alternative.

Studies have shown that compared with PZI and Lente insulin glargine insulin is associated with the highest remission rates. Yet veterinarians often balk at the cost of this human recombinant insulin. One strategy to reduce the cost of insulin and to improve the administration technique is to use an insulin injector pen. The cost of the 3-cc cartridge and pen is about one-tenth the cost of a 10-cc bottle of glargine insulin. Another

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Table 1. Nutrient (Macro) Composition of Feline Therapeutic Diets for Diabetes Mellitus

<table>
<thead>
<tr>
<th>Food Form</th>
<th>Protein</th>
<th>% Dry Matter Carbohydrates</th>
<th>Fat</th>
<th>Crude Fiber</th>
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<td>Hill’s Prescription Diet</td>
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<td></td>
</tr>
<tr>
<td>Feline mid Canned</td>
<td>52.8</td>
<td>15.7</td>
<td>19.4</td>
<td>6.0</td>
</tr>
<tr>
<td>Feline mid Dry</td>
<td>51.1</td>
<td>15.1</td>
<td>21.8</td>
<td>6.0</td>
</tr>
<tr>
<td>Purina Veterinary Diets</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OM Dietetic Management Canned</td>
<td>53.4</td>
<td>4.5</td>
<td>32.9</td>
<td>2.9</td>
</tr>
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<td>14.9</td>
<td>179</td>
<td>1.3</td>
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<td>Royal Canin Veterinary Diet</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetic Dry</td>
<td>46.1</td>
<td>25.3</td>
<td>12.0</td>
<td>4.81</td>
</tr>
<tr>
<td>Diabetic Canned</td>
<td>57.3</td>
<td>15.3</td>
<td>16.4</td>
<td>76</td>
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Measure blood glucose (BG) and serum fructosamine (FR)

<table>
<thead>
<tr>
<th>FR &lt; 400</th>
<th>FR &gt; 400</th>
</tr>
</thead>
<tbody>
<tr>
<td>BG &lt; 180</td>
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</table>

- **EXCELLENT**
- **OWNER INDUCED NONCOMPLIANCE**
- **OVER REGULATION**
- **STRESS-POOR CONT**

Figure 1. Interpretation of blood glucose and serum fructosamine measurements to monitor diabetic dogs and cats.

Option would be to use PZI insulin, which is associated with a lower remission rate (70%) but is easier to administer and less costly. In either case, in my experience, an initial dosage of 2 U per cat twice daily has not been associated with hypoglycemia. For owners who prefer to give oral medication, to monitor cats using blood glucose testing because the stress of a new diet, administration of insulin, and altered home routine make home glucose curves difficult to interpret. Continuous glucose monitors may be more effective in determining if the cat is going into remission or if hypoglycemia is occurring.18-20 The options for treatment include radiation treatment of the pituitary tumor or cryohypophysectomy/hypophysectomy.21-23 New medical therapy for acromegaly may become available in the future, but at present, it is very expensive.

The second most common endocrinopathy found in diabetic cats are glipizide, a sulfonylurea antidiabetic.
agent, has been used to successfully treat diabetes mellitus in cats at a dosage of 2.5 mg twice daily when combined with a high-protein, low-carbohydrate diet.\(^1\)

Monitoring newly diagnosed and treated feline diabetics can be challenging. I prefer to use a slow method of remission induction using urine glucose monitoring at home coupled with periodic (every three weeks) serum chemistry, urinalysis, and fructosamine monitoring. An algorithm for monitoring with serum fructosamine is shown in Figure 7. The owner must agree to not increase the insulin dosage based on urine glucose, and to only decrease the dosage if the urine glucose becomes negative.

Owners are not encouraged

**Complicated feline diabetes** One reason for a cat to fail to go into diabetic remission is a concurrent or most common endocrinopathy associated with hyperinsulinism.\(^2,3\) Acromegaly in cats that do not go into remission or that require increasing dosages of insulin can be suspected by increased interdental spaces. Diagnosis can be made measuring insulin-like growth factor in serum. Confirmation of a pituitary adenoma may be shown on CT.\(^3\) If a cat is diagnosed with acromegaly...
Diabetic cats may have hyperthyroidism. If the wide fluctuations in thyroid concentrations, id cats will be difficult to manage. However, permanent hyperthyroidism may be difficult to manage. Hyperthyroidism should be suspected in female cats with insulin diabetes. Hyperthyroidism can be suspected on the basis of a lack of suppression.
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during a low-dose dexamethasone suppression test, urinary excretion of glucocorticoids, and/or elevated precursors of endogenous ACTH concentrations.

Renal complications of diabetes mellitus are common in human diabetics and may also be common in cats. The earliest sign of diabetic nephropathy is microalbuminuria followed by

Careful attention to diet, good oral health, the addition of probiotics, and judicious use of antibiotics and steroids may all help when managing a cat with concurrent gastrointestinal disease and diabetes.

most successful in treating diabetic nephropathy. Feeding canned food is particularly important in diabetic cats with concurrent renal disease in order to prevent dehydration.

Diabetic cats often have concurrent gastrointestinal disease such as oral disease, pancreatitis, inflammatory bowel disease, and cholangiohepatitis. Some of these gastrointestinal diseases may originate as a result of suppressed immune function (periodontitis); autonomic diabetic neuropathy (diabetes); or possibly as a result of concurrent pancreatitis, cholangiohepatitis, or inflammatory bowel disease. Careful attention to diet (low-carbohydrate Purina Veterinary Diets™ DM Management® or Purina Veterinary Diets™ EN Gastroenteric Formula), good oral health, the addition of probiotics (e.g., Feline Probiotic Nutritional Supplement), and judicious use of antibiotics and steroids (for pancreatitis) may all help when managing a cat with concurrent gastrointestinal disease and diabetes.

Canine diabetes mellitus

Diagnosis of diabetes mellitus in dogs

Insulin-dependent diabetes mellitus is a diabetic state in which endogenous insulin is not produced in sufficient amounts to prevent ketosis. Type 1 diabetes is a diabetic state in which insulin production is absent and which is readily corrected by exogenous insulin. Type 2 diabetes is caused by autoimmune destruction of cells (genetic disorder related to hypothyroidism), and Type 3 (mature onset diabetes of the young) is a non-immune disease.

an increased protein:creatinine ratio in the urine. Azotemia is a late consequence of diabetic nephropathy; however, with good regulation, it may be reversible. Improved diabetic regulation using a canned low-carbohydrate diet and insulin or oral hypoglycemic agents is
of islets caused by 
5 or an unknown cause.',
± at have diabetes mellitus
± from 4 to 14 years, with 
± dence at 7 to 9 years. A
± is for diabetes mellitus
± pected in Samoyeds,
± m, Labrador retrievers,
± terriers (Australian,
± n). Other breeds
affected are miniature and
±, dachshunds, beagles,
± ure schnauzers, and
± nchers. Most dogs with
± llitis present with the
± al signs of polyuria and
± Weight loss and
± are commonly observed in
± with diabetes mellitus are
± only presented with acute
± dness caused by bilateral
± ds, dehydration
± wasting or thin body
± re the most common
± amination findings.
± gly is usually observed,
± ts are observed in about
± betic dogs.
± isis of diabetes
± uld be based on the
± if clinical signs
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± evidence of fasting
± mia and glycosuria.
linicopathologic features of
± llitis in dogs
± ing hyperglycemia,
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± es (ALP, ALT),
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± eria, and glycosuria.

ulent of canine
± llitis
± dogs, the protein
± the diet should be
normal or increased, particularly if the dog is obese. Higher protein formulations may also benefit underweight diabetic dogs with significant muscle wasting or those experiencing concurrent exocrine pancreatic insufficiency. A moderately carbohydrate-

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<tr>
<td>Canine rid Canned</td>
<td>25.3</td>
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<td>Canine wid Dry</td>
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<td>50.8</td>
<td>8.7</td>
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Table 2. Macronutrient Content of Selected Therapeutic Dog Foods Suitable for Diabetic Dogs
moist foods) should not be used to improve the palatability of food prescribed for diabetic dogs. Diets with moderate dietary fiber content are recommended for diabetic dogs (crude fiber maximum 10% to 15% dry matter).

Exercise, if prescribed and regular, may reduce insulin requirements in dogs. The owners should be instructed to walk the dog daily and avoid intermittent episodes of strenuous exercise, such as racing or hiking.

Human recombinant insulin is the most available insulin preparation on the market and is perfectly acceptable as insulin therapy for all dogs. Intermediate-acting insulin (NPH, Lente) or long-acting glargine is administered twice daily in dogs, at a starting dosage of 0.4 to 0.5 U kg⁻¹ day⁻¹. In dogs, the long-acting insulin PZI is administered once or twice daily at 0.8 to 0.9 U kg⁻¹ day⁻¹. Detemir insulin is dosed at 0.1 to 0.2 U/kg twice daily in dogs and may be the insulin of choice for larger dogs. To mimic the physiologic release of insulin, insulin should ideally be given with each meal. If the animal does not eat, the insulin dosage can be reduced (usually by one-half) or skipped entirely and the animal evaluated by the veterinarian to determine the cause of the anorexia.

In general the client should be instructed to monitor the insulin effect and gross regulation of hyperglycemia by noting changes in appetite, attitude, body condition,
polydipsia, polyuria, and urine glucose and ketone levels.
Consistently high urine glucose readings coupled with uncontrolled clinical signs, such as polyuria/ polydipsia, indicate that the insulin dose may be inadequate. Consistently negative readings on urine glucose may indicate that insulin dosages are either adequate or excessive.

Complicated diabetes mellitus in dogs

Hypothyroidism is a common concurrent endocrinopathy in diabetic dogs. The genetic abnormality associated with type 1 diabetes mellitus in dogs is also associated with lymphocytic thyroiditis in dogs. A diagnosis can be made identifying a low or low normal thyroxine concentration and a high endogenous thyroid-stimulating hormone concentration. Hyperadrenocorticism, if present in a diabetic dog, usually precedes the diagnosis of diabetes mellitus as long-standing poorly treated or untreated hyperadrenocorticism can result in secondary diabetes mellitus from insulin resistance. Treatment of the hyperadrenocorticism using mitotane has the best success in my experience.

Concurrent pancreatitis or exocrine pancreatic insufficiency (EPI) is common in diabetic dogs. About 40% of diabetic dogs have a history of pancreatitis, and about 10% may have EPI. Screening newly diagnosed diabetics for both pancreatitis and EPI should be done at the time of diagnosis and again if poor diabetic regulation is encountered. Serum canine pancreatic lipase immunoreactivity (cPLI) and trypsin-like immunoreactivity (Tu) tests are sufficient for screening.

Pancreatitis should be suspected in any diabetic dog that presents with acute onset of vomiting or abdominal pain. EPI is usually subtle; intermittent anorexia and hypoglycemia is more commonly seen than diarrhea or steatorrhea. Treatment with exogenous pancreatic enzymes is recommended if EPI is identified.

Hyperlipidemias are commonly seen in diabetic dogs and may be a consequence of diabetes mellitus, pancreatitis, hypothyroidism, or hereditary hyperlipidemic syndromes (e.g., miniature schnauzers). Dietary fat restriction (<12% on a dry matter basis or <30% ME) is recommended for diabetic dogs with concurrent chronic pancreatitis or persistent hypertriglyceridemia (miniature schnauzers). Foods with a high fat content should not be given to improve the palatability of food prescribed for diabetic dogs. Instead, the low-carbohydrate, low-fat food may be made more palatable with agents such as warm low-fat chicken or beef broth.

Conclusion

The diagnosis and management of diabetes mellitus in cats and dogs is an important aspect of the practice of small animal internal medicine. The purpose of this article was to share some of my experiences in regulating diabetic animals. Clear direction, expectations, and follow-up about the care of their diabetic pet will help reduce owners’ stress and improve the quality of life for these patients."
<table>
<thead>
<tr>
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<td>m/d Canned</td>
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### Macronutrient Content of Selected Therapeutic Foods Suitable for Diabetic Dogs

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<td>52.5</td>
<td>18.3</td>
<td>33.6</td>
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Predictors that cats will come out of remission

re-diabetic state

Predictors
• Fasting BG > 135 mg/dl
• 3 hrs after IVGTT (1g/kg IV) BG > 250 mg/dl
• Diabetic neuropathy
• Obesity – BCS > 8/9
• Feeding dry food or foods > 10% CHO on a DM basis
• Poor follow-up and monitoring

Predictors of remission
• Recent diagnosis
• Ultra-low carbohydrate diet
• Obesity
• Good glycemic control within first 6 months
• Previous glucocorticoid therapy
• Underlying disease or endocrinopathy (Type 3D)
  • Acromegaly
  • Hyperthyroidism
  • Hyperadrenocorticism
• Absence of diabetic neuropathy
• DKA does not affect chance of remission
References
