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Discovering the reasons underlying difficult-to-control diabetes in cats

In the first of a two-part series, an internist reviews the insulin-related, client-related, and patient-related problems that can make a diabetes management regimen ineffective. Here is a step-by-step approach to identifying and addressing problems that underlie cases of poor diabetic regulation in cats.

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Diabetes mellitus is a common endocrinopathy in feline practice. Cats with diabetes can be challenging to monitor and treat because of the complex pathophysiology of the disease and cats' propensity for stress-related hyperglycemia. In addition, the small size of feline patients makes insulin dosing more difficult. This article will review reasons for poor diabetic regulation and outline a logical approach to the difficult-to-treat diabetic cat.

APPROACH TO THE PROBLEM DIABETIC CAT

In general, problems with diabetic control can be categorized as insulin-related, client-related, or patient-related. Although patient-related problems are more common, it is wise to carefully exclude insulin- and client-related issues first, since these are often easily identified and addressed. When insulin- and client-related issues have been ruled out, we then start to look for patient-related problems.

Insulin-related problems

Sudden loss of regulation in a previously well-controlled diabetic may be due to problems with the insulin itself. Even if you have no specific reason to suspect a loss of biologic activity with the insulin, it is always wise to just discard the present bottle and start a new one. Insulin is a peptide and, therefore, can be damaged by exposure to heat or extreme cold. With some insulin types, agitation during shipping

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can also damage the molecule and alter its biologic effects. Another consideration is bacterial contamination; this can occur quickly and result in degradation of the insulin molecules and loss of potency. And lastly, dilution of the insulin can cause problems as the product may behave differently or become unstable. Before conducting an exhaustive and expensive search to identify patient-related problems leading to insulin resistance, it may be worthwhile to replace an older insulin vial with a new, undiluted one.

Insulin options

Most feline diabetics are treated with protamine zinc insulin (PZI), insulin glargine (Lantus—Sanofi-aventis), or a pork Lente product (Vetsulin—Intervet/Schering-Plough Animal Health). Various compounding pharmacies market beef PZI products, but these facilities are not FDA-regulated, and quality control may be a concern. In November 2009, the FDA approved a U40 human-recombinant PZI (ProZinc—Boehringer Ingelheim) for use in cats. It is advisable to switch to this product if a cat receiving compounded PZI becomes unregulated. Dose equivalency may be questionable, so it is prudent to start again with a conservative dose (0.25 units/kg).

The only insulin glargine product currently available is a U100 formulation (*i.e.* each milliliter contains 100 units). Dosing small cats with a U100 product can be difficult, and practitioners may be tempted to dilute the insulin. However, the slow absorption of insulin glargine depends partly on its acidic pH. Dilution will markedly affect the pharmacokinetics and should never be considered. If anything has been added to the bottle, discard it and start again with an undiluted product.

Client-related problems

Probably the biggest client-related problem reflects the technical difficulties of drawing up small doses of insulin. It is helpful to use a 0.3-ml syringe with a U100 insulin. Also, a syringe magnifier may provide some assistance. However, careful instruction about elimination of air bubbles and other methods to ensure accuracy is essential.

It is prudent to watch the client draw up and administer an insulin dose. Watch carefully for problems with the injection technique, such as intradermal injection or a through-and-through injection. Some owners tend to withdraw the syringe while injecting, so the insulin actually ends up lost in the pet's coat. Checking for moisture on the fur after the injection can be helpful, as can experimenting with a different needle size or length. Practicing with 0.9% saline injections is a safe and effective way to train clients and increase their confidence. Shaving a small patch of hair may let clients visualize the needle penetrating the skin and improve accuracy.

You should not need to shave multiple sites unless a client is having difficulty giving injections.

Patient-related problems

There are various ways to monitor diabetic cats. If patients are doing well (that is, they are maintaining optimal body weight with minimal polyuria and no signs of hypoglycemia), measuring serum fructosamine concentrations is an excellent monitoring tool. However, correctly identifying patient-related problems generally requires frequent blood glucose measurements. Serum fructosamine concentrations or urine glucose tests do not provide enough information to reliably identify problems and guide insulin therapy in problem diabetics. Measuring blood glucose concentrations in cats poses some challenges, as many feline patients experience substantial stress-related hyperglycemia. Consequently, blood glucose measurements made in a clinic setting may be a poor reflection of glycemic events at home. In addition, many cats have substantial day-to-day variability in blood glucose measurement—in any environment.¹ As at-home monitoring facilitates the collection of more data points, a more reliable picture may be generated.

Identifying patient-related problems requires frequent blood glucose measurements.

It is for these reasons that many practitioners are now moving away from in-clinic glucose curves on cats.

Instead, clients are taught how to obtain samples from their cats at home. The modern handheld glucometers are easy to use, and many appear to be reliable.² They require only a tiny drop of blood, which can be collected with a lancet or needle from the ear or foot. In addition, studies have confirmed that capillary blood glucose readings are clinically comparable to results from venous sampling.³

Continuous blood glucose monitors may be a useful tool for monitoring hospitalized cats, but the measurements may also be affected by stress hyperglycemia.⁴ Because the receiver unit needs to stay within a few feet of the cat, using this device in the home may be difficult.

It is helpful to categorize patient-related problems into those suggesting poor regulation (*i.e.* substantial fluctuations in blood glucose concentrations or episodes of hypoglycemia) or insulin resistance (*i.e.* excessive amounts of insulin are needed to impact blood glucose concentrations) (Table 1).

Poor regulation. Poorly regulated patients require frequent adjustments to their insulin dose or experience episodes of clinical hypoglycemia or dramatic changes in blood glucose

TABLE 1

Common Patient-Related Causes of Poor Diabetic Control in Cats

Poor regulation

Energy utilization problems
Energy intake changes
Insulin absorption variability
Insulin kinetics inconsistency
Anti-insulin antibodies
Drugs and other diseases

Insulin resistance

Obesity
Hyperlipidemia
Endocrinopathies—hyperthyroidism,
hyperadrenocorticism, growth hormone excess
Infection or other diseases—urinary tract infection,
periodontal disease
Inflammation—chronic pancreatitis
Medication—glucocorticoids, progestins
Anti-insulin antibodies

concentrations during the day. In most cases, problems with energy (either utilization or intake) or the biological behavior of the insulin are the cause. However, an additional consideration in feline patients is the onset of diabetic remission.^{5,6} This commonly occurs in newly diagnosed diabetic cats; failure to identify the onset of remission may result in life-threatening insulin overdose. This possibility should always be considered in a hypoglycemic cat, particularly within the first three months of diagnosis. Careful blood glucose monitoring is needed to identify this event and to permit safe tapering of the insulin dose.

Compared with canine patients, problems with unexpected energy utilization are uncommon because cats are inherently sedentary. However, I have observed hypoglycemic collapse in a well-regulated diabetic cat after an energetic play session with a visiting child.

Similarly, a change in energy intake due to the feeding of snacks or treats is rarely an issue with our feline diabetics. However, a sudden change in diet type (such as a switch to a high-carbohydrate food) may result in poor glycemic control. Careful questioning of clients about compliance with dietary recommendations is certainly appropriate.

Problems with insulin absorption should be considered if the insulin has an erratic effect, particularly if the onset of action seems to vary from day to day. This may be due to tissue irritation at the injection site, in which case rotating through six to eight locations may solve the problem. The other consideration is the insulin type. PZI products have an innately lower bioavailability than other types, with less predictable glycemic results.⁷

The term *insulin kinetics* refers to the biological behavior of an insulin product. As a species, cats have unique responses to both food and insulin; treating a cat like a small dog often results in poor regulation. For example, postprandial hyperglycemia does not occur in cats fed typical cat foods, so feline diabetics are often fed ad libitum.⁸ In addition, the calorie source within a feline diabetic's diet has a profound influence on its insulin requirements, and cats eating high-protein diets require less insulin.⁹

Although most diabetic cats respond to Lente insulin, this type generally has a shorter duration of effect in cats than in dogs. Consequently, twice-daily dosing may result in long periods of inadequate glycemic control and substantial hyperglycemia before the next injection.¹⁰ A switch to a long-acting product such as insulin glargine is an appropriate option for this problem. (See Table 2 for an example.)

Traditionally, PZI products are a popular choice for feline diabetics and are often regarded as appropriate for once-daily dosing. Some cats do appear adequately controlled with once-daily therapy, which may be regarded as an advantage by some clients.¹¹ However, in many individuals twice-daily therapy seems to provide the best glycemic control.¹² A 24-hour glucose curve is the best way to identify the true behavior of

this product in an individual cat, as the absorption kinetics, peak effect, and duration of action are unpredictable.⁷

The very long-acting products such as insulin glargine are now emerging as a suitable choice for feline diabetics.¹⁰ Insulin glargine has a gradual onset of effect but often lasts more than 24 hours.¹³ However, twice-daily dosing is suggested to maintain a euglycemic state. Because of its specific biochemical attributes, practitioners need to learn new parameters for dose adjustments with this product. One of the crucial concepts is the slow response; it may take two to three days to see a change in blood glucose concentrations after initiation of therapy or after a dose increase. Serious problems can occur if the dose is stepped up aggressively without allowing time to determine the effect. One of the advantages of insulin glargine is that most cats experience only minor fluctuations in blood glucose concentrations over the course of the day, and a reliable picture of glycemic control can be obtained with a blood glucose measurement taken every four hours. If possible, have the owner check blood glucose concentrations at home for the first three days so that hypoglycemia can be identified.

Little clinical data address the issue of anti-insulin antibodies in feline diabetics. In theory, antibodies generated against heterologous insulin may cause trapping of insulin at the injection site with subsequent compromised release from the subcutaneous tissues or overt insulin resistance (see below).¹⁴ Feline insulin is most similar to bovine insulin, whereas human insulin is less similar. However, as many cats are adequately

regulated for long periods on insulin glargine (which is based on the human molecule) or porcine Lente insulin, it seems unlikely that anti-insulin antibodies have a marked impact on most feline diabetics.⁶ The only beef insulins currently on the market are compounded PZI products. Although there are concerns about quality control with these products, it may be useful to try these in a poorly regulated cat if the common causes of insulin resistance have been excluded.

Insulin resistance. There is no clear definition of insulin resistance, but most clinicians regard a cat as resistant to insulin if a dose exceeding 1.5 units/kg fails to bring the blood glucose concentration below 300 mg/dL.¹⁴ There are several different reasons for insulin resistance in feline patients, and various different biochemical mechanisms may be involved (Table 1).

Obesity is a common cause of insulin resistance in cats and probably plays a role in the development of diabetes in many patients. Adipose tissue is highly metabolically active and releases numerous chemicals (e.g. adiponectin, leptin) that directly impact the effect of insulin.^{15,16} Controlled weight loss is essential in obese cats, with a target loss of 1% to 2% per week. In addition to calorie restriction, the nature of the ingested energy must be considered. Low-carbohydrate, high-protein diets are now recommended for diabetic cats, as improved glycemic control has been documented.^{9,17}

Concurrent infections are commonly noted in feline diabetics and can certainly impact these cats' response to insulin. Urinary tract infections appear to be prevalent in diabetic cats, particularly females, with an 18% incidence cited in one recent report.¹⁸ Clinical signs of lower urinary tract disease may be noted by the client, but the possibility of a urinary tract infection should not be discounted simply because the cat is not dysuric, pollakiuric, or hematuric.

If an insulin-resistant cat has severe periodontal disease, it may be advantageous to address this problem. Chronic infection in the mouth may trigger the release of counter-regulatory hormones such as cortisol, with resultant persistent hyperglycemia.

Sterile inflammatory diseases cause insulin resistance through a similar mechanism. Pancreatitis, particularly the chronic form, appears to be common in feline diabetics. The feline pancreas-specific lipase activity test (Spec fPL—IDEXX Laboratories) has a high sensitivity and specificity in moderate to severe pancreatitis but may yield normal results in cats with mild forms of the disease.¹⁹ Abdominal ultrasonography is also a useful tool for evaluating pancreatic inflammation in cats. Managing cats with pancreatitis can be difficult, but pain control and nutritional support are often beneficial. Some cats with chronic pancreatitis develop exocrine pancreatic insufficiency. This is best identified with a trypsin-like immunoreactivity determination and then managed with powdered enzyme products.²⁰

TABLE 2

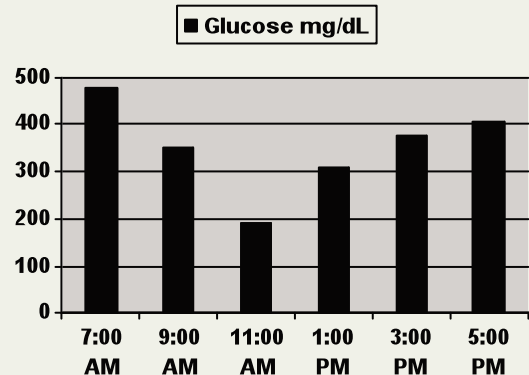
VETERINARY
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Case Example

Signalment: 9-year-old 4.3-kg castrated male domestic shorthaired cat

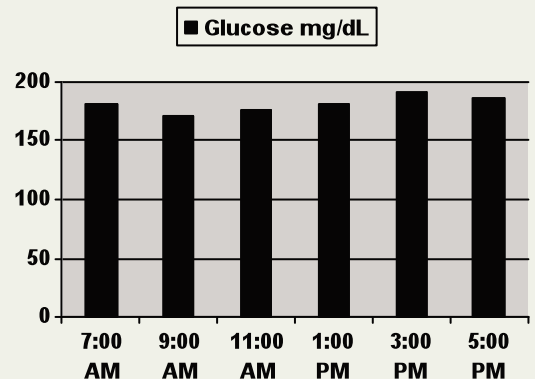
Chief complaint: Poor diabetic regulation

History: Diabetic for three months; initially started receiving Lente insulin, but clinical signs have persisted. Cat is losing weight and now has a plantigrade stance in the rear. Presently receiving 2 units (0.5 units/kg) b.i.d.



Interpretation: Early glucose nadir (four hours) due to short duration; average glucose > 250 mg/dl over the day.

Plan: Start glargine at 1 unit (about 0.25 units/kg) b.i.d.



Recheck visit 14 days later: Patient is clinically improved with minimal polydipsia and polyuria

Interpretation: Excellent control of blood glucose

Plan: Continue glargine b.i.d.

TABLE 3

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Suggested Workup for Insulin-Resistant Diabetic Cats

STEP 1 Review history and physical examination findings.

STEP 2 Thoroughly review concurrent medications.

STEP 3 Perform routine CBC, serum chemistry panel, urinalysis, and T₄.

- Evaluate for occult or concurrent disorders
- Measure free T₄ ED if T₄ is borderline

STEP 4 Perform a urine culture.

STEP 5 Consider performing the Spec fPL.

- Particularly if appetite is variable

STEP 6 Consider serum cobalamin measurement.

- Particularly if appetite is variable

STEP 7 Consider fTLI.

- Particularly if stools are soft

STEP 8 Consider dental cleaning if the oral examination findings are supportive.

STEP 9 Consider acromegaly.

- Particularly if the cat is gaining weight
- Measure IGF-1 or GH

STEP 10 Consider hyperadrenocorticism.

- Particularly if skin changes are noted
- Perform LDDST

STEP 11 Perform a more extensive search for occult systemic disease.

- Thoracic radiography
- Abdominal ultrasonography

cats, namely polyphagia, weight loss, polyuria, and polydipsia, mimic those of uncontrolled diabetes mellitus, which can lead to delayed recognition. In most cases, hyperthyroidism is easily confirmed by an increase in basal serum thyroxine (T₄) concentration; however, this concentration may remain within the reference range in early cases. If the T₄ is above the middle of the reference range in a poorly regulated diabetic cat, it may be helpful to measure free T₄ by equilibrium dialysis (ED). This is not recommended as a screening test, however, as some euthyroid cats have modest increases in free T₄ ED.

Acromegaly due to a pituitary adenoma is a well-recognized cause of insulin resistance in cats.^{22,23} Progressive weight gain despite poor diabetic regulation is a hallmark. Specific physical changes, such as enlargement of the tongue and feet or separation of the incisors, are often seen later in the disease. Recent studies have shown that measurement of serum insulinlike growth factor-1 (IGF-1) is a useful screening test for cats, although an elevated concentration may not be definitive.^{24,25} The University of Minnesota offers a feline growth hormone assay that may be more useful, although there is little information available regarding this test. If either GH or IGF-1 concentrations are supportive of acromegaly, the next step would be imaging of the pituitary region (with either computed tomography or magnetic resonance) to identify a mass.²⁶

Hyperadrenocorticism is much less common in cats than in dogs, but it is associated with profound insulin resistance. Cats can develop this disease as a result of oversecretion of adrenocorticotrophic hormone (ACTH) by the pituitary gland or a functional adrenocortical tumor. Again, many of the clinical signs (e.g. excessive thirst and appetite) associated with hyperadrenocorticism mimic those of uncontrolled diabetes. Therefore, practitioners should pay careful attention to physical changes such as loss of abdominal muscle mass or skin fragility, as these strongly suggest hyperadrenocorticism.²⁷ The most reliable diagnostic test for suspect cats is the low-dose dexamethasone suppression test (LDDST). The dose of dexamethasone used for the LDDST in cats is 0.1 mg/kg, which is much higher than the canine dose. Abdominal ultrasonography is often the easiest way to identify an adrenal tumor. If both adrenal glands are enlarged, pituitary imaging should be considered.

Concurrent medications should always be carefully evaluated in insulin-resistant cats. Glucocorticoids and synthetic progestins, such as megestrol acetate and medroxyprogesterone acetate, are potent insulin antagonists.²⁸ As mentioned earlier, anti-insulin antibodies should also be considered in a cat with insulin resistance.

SUMMARY

The difficult diabetic cat poses some unique challenges, but careful data collection and patient evaluation will often uncover the cause of poor glycemic control. A step-wise, logical approach should be followed (*Table 3*) so that straightforward

Another important consideration is concurrent endocrinopathies. Hyperthyroidism is a prevalent endocrine disorder in geriatric cats and may impact the effectiveness of exogenous insulin.²¹ Many of the signs seen with thyroidal disease in

problems are effectively addressed before more complex diagnoses are considered. ❖

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