

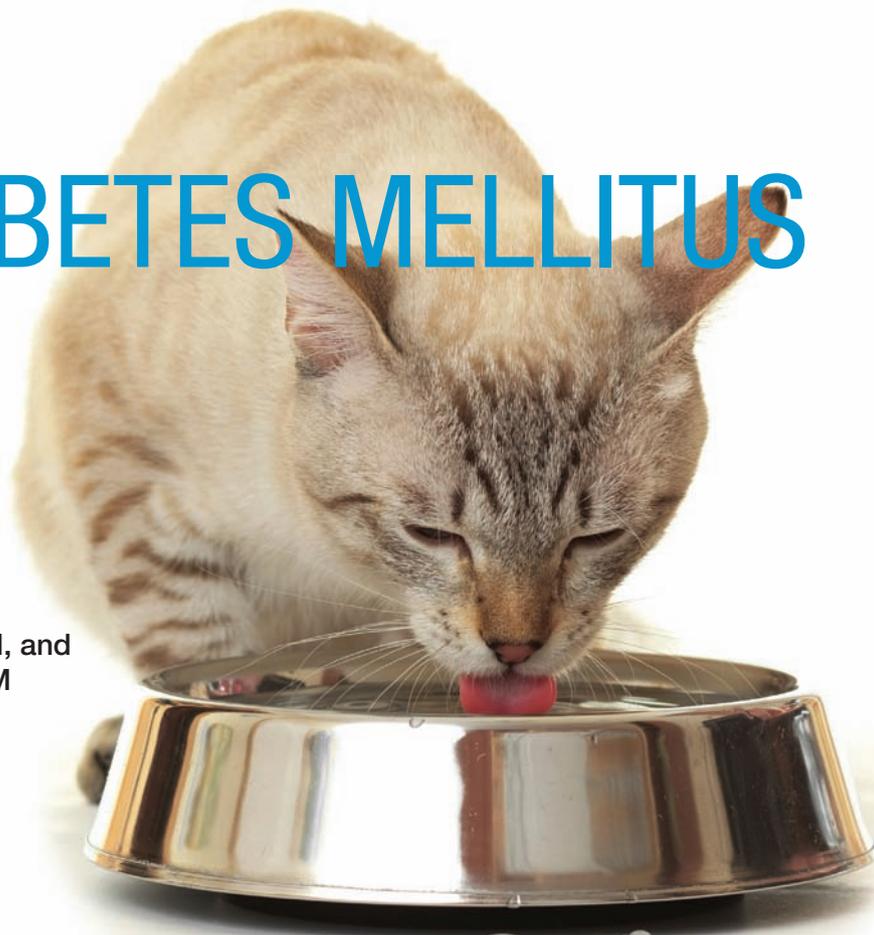
FELINE DIABETES MELLITUS

Updates on Diagnosis & Treatment

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**Feline
Friendly
Article**



Diabetes mellitus (DM) is a commonly encountered feline endocrine disease.¹ DM is defined as *persistent hyperglycemia and glycosuria due to an absolute or relative insulin deficiency*. The most common causes of feline DM are:

- Islet cell amyloidosis
- Obesity
- Chronic pancreatitis.

CLASSIFICATION

Insulin is secreted exclusively from beta cells in the pancreas' Islets of Langerhans. Insulin deficiency occurs when beta cells are destroyed or their function impaired, and the pathogenesis of beta cell dysfunction is used to classify DM.

In humans, DM is classified as:

- **Type I (insulin dependent):** Results from autoimmune damage to the Islets; associated with complete lack of insulin
- **Type II (noninsulin dependent):** Characterized by abnormal insulin secretion and peripheral insulin resistance
- **Gestational, congenital, neonatal, or monogenic.**

Most feline diabetics have type II DM,² and may have underlying susceptibilities to this type due to genetic predisposition and decreased insulin sensitivity (seen with obesity).^{3,4}

Type III DM is similar to impaired glucose tolerance in humans. Medications or diabetogenic hormones (epinephrine, cortisol, glucagon, and growth hormone) interfere with the action of insulin, result in glucose intolerance, and ultimately lead to DM. This is in dis-

tinction to Type II DM in which the cause of insulin resistance is often unknown.

PATHOGENESIS

Amylin, also known as *islet amyloid polypeptide* (IAPP), is synthesized in the Islets of Langerhans and co-secreted with insulin. In cats with insulin resistance, amylin and insulin secretion increase concurrently. Over time, amylin overproduction progresses to diabetes due to 2 phenomena:

1. Amylin can be enzymatically converted to amyloid, which has a direct cytotoxic effect on islet cells.⁵
2. In addition, amylin itself inhibits further insulin secretion in a paracrine effect.⁵

Both contribute to initial glucose intolerance and, eventually, overt hyperglycemia and glucosuria.

DIAGNOSIS

DM is diagnosed based on clinical signs and laboratory testing.

Clinical Signs

DM is typically diagnosed once blood glucose (BG) exceeds renal threshold (mean threshold, 290 mg/dL⁶), resulting in osmotic diuresis and compensatory polydipsia. Other classical clinical signs include polyphagia and weight loss.

Basic Laboratory Evaluation

Baseline laboratory evaluation should include a serum biochemistry profile, CBC, urinalysis, and urine culture. Diabetic patients frequently have urinary tract

TABLE 1. Feline Diabetes Mellitus: Common Biochemical Abnormalities & Causes

Test	Abnormalities	Cause
Complete Blood Count	Often unremarkable Hemoconcentration	Dehydration
Serum Biochemical Profile	Elevated alanine transaminase Elevated alkaline phosphatase Elevated bilirubin Hyperglycemia	Biliary disease/ pancreatitis Hepatic lipidosis/ hepatitis Pancreatitis/lipidosis
Urinalysis	Active sediment (indicating infection) Glucosuria Ketonuria	Urinary tract infection Blood glucose in excess of renal threshold Ketogenesis

infections even in the absence of active urine sediment (Table 1).⁷

Transient hyperglycemia may be caused by stress, diabetogenic hormones, and post prandially in animals with glucose intolerance. Cats are particularly sensitive to stress hyperglycemia due to catecholamine release.⁸

Fructosamine Evaluation

Fructosamine is formed when glucose reacts with amino acids of serum proteins, such as albumin. In hyperglycemic states, levels of fructosamine increase. Fructosamine levels can be used for several purposes:

- **To help confirm a diagnosis of DM**
- **To monitor persistent hyperglycemia;** levels above the reference range indicate persistent hyperglycemia and, therefore, help differentiate diabetes from other causes of transient hyperglycemia.
- **To evaluate response to treatment;** in well-controlled diabetics, fructosamine is often in the low end of the reference range or normal.

Total Thyroxine Evaluation

Total thyroxine levels should be evaluated to rule out hyperthyroidism as a cause for insulin resistance.

INSULIN OVERVIEW

Several types of insulin are available for use in diabetic cats.

- **Ultra long acting:** Glargine (Lantus, sanofi.us) and

CLINICAL SIGNS OF CONCURRENT/ SECONDARY DISEASE

- Cats may present with **icterus** due to concurrent *hepatic lipidosis* or *pancreatitis*.
- A **plantigrade stance** may be noted secondary to prolonged or severe hyperglycemia, resulting in a *peripheral neuropathy*.

detemir (Levemir, novonordisk-us.com)

- **Long acting:** Human recombinant protamine zinc (PZI) (ProZinc, boehringer-ingelheim.com)
- **Intermediate acting:** Lente (Vetsulin, merck.com), which was recently reintroduced to the veterinary market, and neutral protamine Hagedorn (NPH) (Humulin N, lilly.com, or Novolin N, novonordisk-us.com).

For dosing recommendations, see Table 2, page 12.

ULTRA LONG-ACTING INSULINS

Glargine

Glargine is a long-acting insulin analogue that is designed to provide basal insulin concentrations in humans. It remains soluble in acidic solutions but forms precipitates in the neutral environment of subcutaneous tissue. The change in pH associated with precipitation contraindicates diluting or mixing glargine for administration.

Efficacy. Glargine has been shown to be effective in felines with DM. A recent study compared the glycemic control and remission probabilities in 24 newly diagnosed diabetic cats treated twice daily with either glargine, PZI, or lente insulin and fed a low-carbohydrate diet.⁹

- Probability of remission was substantially higher for cats with lower mean 12 H BG concentrations on day 17, irrespective of insulin type.⁹
- In this small study, cats treated with glargine had better glycemic control and higher probability of remission than those treated with PZI or lente insulin.⁹ However, further studies with larger numbers of cats are needed before it can be concluded that glargine is more effective at achieving remission than other insulins.
- In a different study of owner responses on an online forum, a remission rate of 84% was noted in patients treated with glargine within 6 months of diagnosis; cats treated with glargine 6 months after diagnosis achieved a 35% remission rate. Caution should be exercised not to overinterpret owner reports that were not confirmed by a veterinarian.¹⁰

GOALS OF TREATMENT

- Minimize clinical signs
- Avoid complications, such as diabetic ketoacidosis and peripheral neuropathy
- Avoid symptomatic hypoglycemia
- Maintain owner compliance with treatment regimen and follow-up
- Achieve patient quality of life
- If possible, achieve diabetic remission



Diabetic remission is defined as *the ability to maintain euglycemia without insulin for 2 to 4 weeks after insulin therapy has been discontinued, without the reappearance of clinical signs of diabetes.*

Remission appears more likely to occur if:

- Blood glucose levels are strictly controlled using insulin
- Cats are fed a low-carbohydrate diet.

At least 25% to 30% of cats that have achieved remission subsequently relapse into overt diabetes and need reinstatement of insulin treatment. In these cats, a second remission is unlikely to be achieved and permanent insulin therapy is usually needed.

Good glycemic control soon after diagnosis is associated with increased probability of remission and should be the goal of insulin therapy.^{10,11}

Monitoring. Because glargine is a basal insulin, 4-hour post injection BG monitoring can be performed. If performing a 12-hour BG curve (BGC), samples can be drawn every 4 hours. This type of monitoring is inappropriate for nonbasal insulins, such as NPH or recombinant PZI.

- **Increase** insulin dose by 1 unit Q 12 H if:
 - » Pre-insulin BG concentration is **> 216 mg/dL and/or**
 - » Nadir BG concentration is **≥ 180 mg/dL** (often at 4-hour post insulin injection).
- **Maintain** insulin dose if:
 - » Pre-insulin BG concentration is **180 to 216 mg/dL and/or**
 - » Nadir BG concentration is **90 to 160 mg/dL** (4-hour post insulin injection).
- **Decrease** insulin dose by 1 unit Q 12 H if:

- » Pre-insulin BG concentration is **≤ 180 mg/dL and/or**
- » Nadir BG concentration is **54 to 90 mg/dL** (4-hour post insulin injection).
- » *If the nadir BG concentration is < 54 mg/dL, the next dose of insulin can be skipped rather than taking the chance of an overdose. If the total insulin dose is already 1 unit Q 12 H, stop the insulin (or administer 1 unit Q 24 H) and evaluate for diabetic remission.*

Additional Notes. The manufacturer recommends discarding opened vials after 4 weeks of use; however, if refrigerated, opened vials can be used for 6 months (unless discoloration is noted).

DETEMIR

Detemir, like glargine, is a basal human insulin analogue and binds reversibly to albumin, resulting in a long duration of action. It has been demonstrated to be effective in the treatment of feline DM and is also associated with remission in cats that receive at-home, intensive BG monitoring.

Efficacy. Another recent study of owner results collected through an online forum evaluated detemir and a protocol of intensive BG control with home monitoring in diabetic cats, and compared the results with a previous study that used the same protocol with glargine.¹²

- The study included 18 cats diagnosed with diabetes and previously treated with other insulins.
- No significant differences were identified between the glargine and detemir studies, with the exception of 3 possibly interrelated factors:
 1. Slightly older median age of the detemir cohort at diabetes diagnosis
 2. Higher rate of chronic renal disease in the detemir cohort
 3. Lower maximal dose for detemir.
- Overall remission rate was 67%; cats that began the protocol before or after 6 months of diagnosis had remission rates of 81% and 42%, respectively.

• However, once again, caution should be exercised not to overinterpret owner reports that were not confirmed by a veterinarian.

Administration. In contrast to dogs, detemir does not appear to be more potent than glargine; therefore, the starting dose is the same for both insulins in cats.¹²

Monitoring. Although detemir is a basal insulin, studies have not been performed to evaluate spot BG monitoring. Therefore, BGCs should be performed and BG monitored every 2 hours when using this type of insulin.

TABLE 2. Dosing Recommendations for Insulin Use in Diabetic Cats

INSULIN	TYPE	STARTING DOSE	SYRINGE*
Detemir	Ultra long acting; human insulin analogue	0.5 IU/kg SC Q 12 H	U-100
Glargine	Ultra long acting; human insulin analogue	Fasting BG < 360 mg/dL: 0.25 IU/kg SC Q 12 H Fasting BG > 360 mg/dL: 0.5 IU/kg SC Q 12 H <i>Starting dose not to exceed 3 IU/cat SC Q 12 H</i>	U-100
PZI	Long acting; Human recombinant insulin approved for use in cats	1–2 IU/cat SC Q 12 H	U-40
Lente	Intermediate acting; porcine insulin approved for use in dogs and cats	0.25–0.5 IU/kg SC Q 12 H	U-40
NPH	Intermediate acting; human recombinant insulin	0.25 IU/kg SC Q 12 H or 1–3 IU/cat SC Q 12 H	U-100

*Note: It is critical to use the correct insulin syringe with the concentration of insulin.

LONG-ACTING INSULINS

Protamine Zinc Insulin

Human recombinant PZI has been demonstrated to be effective and is approved for use in cats (ProZinc, boehringer-ingelheim.com).^{13,14} Zinc is added to the protamine to prolong duration of action.

Efficacy. In a large clinical trial, 133 cats were treated with PZI twice daily for 45 days.¹³

- Glycemic control was assessed by evaluating change in water consumption, frequency of urination, appetite, body weight, and serum fructosamine concentration.
- BG concentrations were determined 1, 3, 5, 7, and 9 hours after administration of PZI. Adjustments in PZI dosage were made as needed to control glycemia.
- PZI administration resulted in a significant decrease in 9-hour mean BG and serum fructosamine concentrations and a significant increase in mean body weight (day 45 compared with day 0).

By day 45:

- Polyuria and polydipsia had improved in 79% of cats and 89% had good body condition.
- Nine-hour mean BG concentration, serum fructosamine concentration, or both had improved in 84%.
- Hypoglycemia (< 80 mg/dL) was identified in 151 of 678, 9-hour serial BG determinations and in 85 of 133 diabetic cats. Hypoglycemia resulting in clinical signs was confirmed in 2 diabetic cats.

Administration. PZI is effective for controlling glycemia in diabetic cats and can be used as an initial or alternative treatment in diabetic cats that do not respond to treatment with other insulin preparations. Starting dose is 1 to 2 IU/cat Q 12 H.¹⁴

INTERMEDIATE-ACTING INSULINS

Lente

Lente, which is of porcine origin and contains zinc, is approved for dogs and cats, and has recently been reintroduced to the market (Vetsulin, Merck.com).

Efficacy. A prospective, multicenter, nonblinded study evaluated 46 diabetic cats during treatment with porcine lente insulin (also known as porcine insulin zinc suspension) for 16 ± 1 weeks (stabilization phase), with additional monitoring of some cats (*n* = 23) for a variable period.¹⁵

- At least 3 of the following were present at initial presentation:
 - » Appropriate history of clinical signs consistent with DM
 - » Glucosuria
 - » BG > 15 mmol/L
 - » Fructosamine > 380 micromol/L
- Insulin treatment was started at a dose rate of 0.25 to 0.5 IU/kg Q 12 H, with a maximum starting dose of 2 IU/injection.
- Results of the study included:
 - » 28 cats reached clinical stability during the study; 23 during the stabilization phase

- » 7 cats went into remission during
- » the stabilization phase and one during week 56
- » In 9 of 46 cats, signs of hypoglycemia, which were significantly associated with a dose of 3 IU or 0.5 IU/kg (or more) twice daily, were observed; concomitant biochemical hypoglycemia was recorded in most cases.

Administration. The protocol used in this study is suitable for and easy to use in practice.

Additional Notes. An important change that occurred with the relaunch of Vetsulin is the manufacturer recommends that Vetsulin be shaken thoroughly until a homogeneous, uniformly milky suspension is obtained. Foam formed during shaking should be allowed to disperse before use and, if required, the product should be gently mixed to maintain a homogeneous, uniformly milky suspension before use. Clumps or white particles can form in insulin suspensions: do not use the product if these persist after thorough shaking. Other types of insulins should be mixed gently, not shaken.

The product has a shelf life of 12 months and is usable for 42 days once the vial has been opened.

Note that Vetsulin has amorphous insulin in it, which brings on an earlier peak action time. Therefore, glucose curves should be carefully monitored, especially in the first 2 to 6 hours after administration.

Neutral Protamine Hagedorn

NPH is an intermediate-acting human insulin that contains zinc and has been used more frequently in dogs than cats. There is little data to support its use in cats, and it is not approved for use in cats.

NONINSULIN TREATMENTS

Glipizide

Glipizide is a second-generation sulfonylurea derivative administered orally. Sulfonylurea drugs bind the beta cell ATPase, which stimulates insulin release.

Effectiveness of treatment with this class of drugs depends on functional beta cells. Therefore, in cats

INSULIN RESISTANCE

Insulin resistance in cats is typically defined as an insulin dose > 1.5 IU/kg or 6 IU per dose. The most common causes of insulin resistance are:²¹⁻²⁴

- Bacterial infections
- Heart failure
- Hyperthyroidism
- Obesity
- Pancreatitis
- Renal failure.

Severe insulin resistance and marked hyperglycemia, despite high dose insulin, can be caused by:

- Excess glucocorticoids
- Acromegaly or excess growth hormone
- Progestagens.

suffering from beta cell exhaustion or glucose toxicity, response can be variable.

Side effects can include vomiting, hepatotoxicity, and hypoglycemia. In addition, insulin secretion stimulated by sulfonylurea drugs has been accompanied by concurrent amylin secretion,¹⁶ which may result in further damage to beta cells.

Due to variable response rates and side effects its use is not typically recommended.

Glyburide

Glyburide is a second-generation sulfonylurea drug with a longer duration of action than glipizide. It has been evaluated in normal cats and resulted in the release of insulin. Both sulfonylureas may result in progression of diabetes due to increased production of IAPP and its subsequent conversion to amyloid in the pancreatic islets.¹⁶

Chromium Picolinate & Vanadium

Chromium picolinate is a trace element and cofactor for the function of insulin. It increases both insulin binding and number of insulin receptors. Chromium deficiency can lead to insulin resistance; in humans, supplementation has been shown to improve glycemic control.¹⁸

Vanadium is another trace element that has glucose-lowering effects and may improve insulin secretion and glucose metabolism.

Studies in cats have shown little efficacy of chromium or vanadium in controlling clinical signs of DM.¹⁷

Exenatide

Exenatide (Byetta, amylin.com), a glucagon-like peptide-1 mimetic, is an injectable medication that plays a role in treatment of DM by stimulating insulin release. Other potential benefits include:

- Delayed gastric emptying, which blunts post prandial hyperglycemia
- Appetite curbing
- Promotion of beta-cell regeneration by inhibition of beta cell apoptosis.

Exenatide was studied in healthy cats and shown to affect insulin secretion in a glucose dependent manner.¹⁸

DIET

Low-carbohydrate/high-protein diets are recommended for diabetic cats.

- Canned wet foods are preferable to kibble because they contain lower carbohydrate concentrations.
- Ideally, cats should be fed twice daily at the time of insulin injection. However, the timing of meals is not as critical in cats as it is in dogs due to lack of prolonged post-prandial hyperglycemia.¹⁹

- Insulin resistance is affected by obesity; therefore, in order to achieve and maintain remission, an ideal body weight is recommended.

AT-HOME MONITORING

In-clinic BGCs are more likely to be affected by stress hyperglycemia than BGCs generated at home. Veterinarians should be cautious of responding to high glucose results by overzealously increasing insulin doses. Monitoring strategies may be influenced by persistence or resolution of clinical signs.

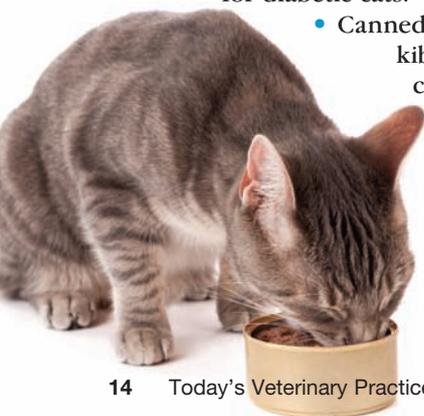
A pressing concern for the newly diagnosed and treated cat is the possibility of development of hypoglycemia in individuals that may quickly go into remission. This can be addressed by using an at-home glucometer that is accurately calibrated for cats at the low end of the reference range.²⁰

AlphaTRAK (abbottanimalhealth.com) is a species-specific glucometer calibrated for feline and canine patients. Use of human glucometers can lead to inaccurate readings and falsely low blood glucose values when used in dogs and cats. ■

BG = blood glucose; BGC = blood glucose curve; DM = diabetes mellitus; IAPP = islet amyloid polypeptide; NPH = neutral protamine Hagedorn; PZI = protamine zinc insulin

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