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**Part 2: Treatment**

# Diabetes Mellitus

Diagnosis of diabetes mellitus was discussed in Part 1 of this article, published in the October issue of *Clinician's Brief* and available at [cliniciansbrief.com](http://cliniciansbrief.com).

 **Medications**

**Insulin**

Intermediate- and long-acting insulins are used for long-term management of diabetes mellitus (DM).

**Intermediate-Acting Insulins**

- *Neutral protamine Hagedorn (NPH)* (Humulin N, elanco.com; Novolin N, norvonordisk.com): Validated in dogs and cats, but not approved for use by the FDA<sup>1,2</sup>
- *Purified porcine insulin zinc* (Vetsulin & Caninsulin, intervet.com): The only insulin

product currently FDA approved for use in dogs and cats<sup>3,4</sup>

- *Protamine zinc insulin (PZIR)* (ProZinc, boehringer-ingelheim.com): In final stages of review by the FDA and expected to be approved for cats by end of this year; studies reported in cats<sup>5</sup>

**Longer-Acting Insulins**

- *Glargine insulin* (Lantus, sanofi-aventis.us): Studies reported are mainly in cats; not FDA approved for use in dogs or cats<sup>6</sup>
- *Detemir insulin* (Levemir, norvonordisk.com): Preliminary studies reported in

cats; not FDA approved for use in dogs or cats

**Administration**

All intermediate-acting insulins should be started at a dose of 0.5 U/kg Q 12 H.<sup>1,3,6</sup> Longer-acting insulins should also be started at 0.5 U/kg.

Dogs almost always require twice-daily insulin. Some cats receiving longer-acting insulins may be treated effectively with once-daily injections, but most cats require twice-daily injections, even when treated with longer-acting insulins.

DM = diabetes mellitus; NPH = neutral protamine Hagedorn; PZIR = protamine zinc insulin

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Veterinary insulin products (porcine insulin zinc, PZIR) are produced in U40 formulations and must be administered with U40 syringes. Human insulin products (NPH, glargine, detemir) are produced in U100 formulations and must be administered with U100 syringes.

**Contraindications & Precautions**

Insulin can cause hypoglycemia if the dose is too high, a cat or dog has transient DM and no longer requires insulin, the patient did not eat its entire meal but received a full dose of insulin, or the patient exercised excessively without gradual adjustment of diet and insulin.

Mistakenly administering a human insulin product with a U40 syringe results in insulin overdose and may cause potentially fatal hypoglycemia. Administering a veterinary insulin product with a U100 syringe results in insulin underdose and the animal could potentially develop complications such as diabetic ketoacidosis.

**Glipizide**

Some cats with mild hyperglycemia and no significant concurrent disease may respond well to treatment with an oral hypoglycemic medication. The sulfonyleurea glipizide, which stimulates insulin secretion from pancreatic beta cells, is the oral hypoglycemic most studied in diabetic cats. One study<sup>7</sup> found that 14% (7/50) of cats with uncomplicated DM responded well to treatment with glipizide alone. Potential side effects of glipizide include vomiting shortly after administration, hypoglycemia, increased serum hepatic enzyme activities, and icterus.

**Administration**

- 2.5 mg/cat PO Q 12 H for 2 weeks
- If adverse side effects are not observed by the end of 2 weeks and the cat is still hyperglycemic, the dose is increased to 5 mg/cat PO Q 12 H.

- If blood glucose concentration remains above 300 to 400 mg/dL after 4 weeks, treatment is discontinued and insulin is administered.

**Tx Additional Treatment**

**Activity**

Exercise promotes weight loss in obese patients and increases glucose transport and glycogen synthesis. Moderate consistent exercise is recommended at fixed times and patients should be conditioned to exercise gradually. Intense exercise, especially when blood glucose may be low, should be avoided.

**Nutrition**

Caloric intake should be timed at 12-hour intervals, at a fixed time every day, just prior to insulin injections. The amount of food fed at each meal should also be fixed. If cats do not agree to eat 2 meals a day, they must have food available throughout the day. However, it is useful to offer enticing (appropriate) additional food at 12-hour intervals, just prior to insulin injections.

In dogs, a diet high in insoluble fiber (Prescription Diet w/d, hillspetnutrition.com; Veterinary Diets DCO, purina.com) promotes weight loss, gradual carbohydrate absorption, decreased postprandial blood glucose fluctuations, and increased insulin sensitivity.<sup>8</sup> Complex carbohydrates and a fixed protein and restricted fat content also contribute to gradual carbohydrate absorption and decreased postprandial blood glucose fluctuations as well as weight loss.

Diabetic cats are fed a fixed caloric intake of a diet low in carbohydrate content and high in protein (Veterinary Diets DM, purina.com; Prescription Diet m/d, hillspetnutrition.com) with the intent of maintaining optimal body condition.<sup>9</sup>



**Client Education**

Diabetic animals require life-long, intensive home care as well as constant veterinary monitoring. Owners should:

- Note changes in clinical signs suggestive of hyperglycemia (polyuria/polydipsia, weight loss in spite of good appetite)
- Recognize signs of severe hypoglycemia (ie, seizures, weakness, ataxia). If such signs are observed, the owner can rub corn syrup on the gums until emergency veterinary care can be administered.
- Monitor urine glucose Q 12 H before feeding.
- Note presence or absence of ketones in urine Q 12 H. Ketonuria constitutes an emergency.
- Administer half the dose of insulin and seek veterinary advice if the patient vomits or does not eat its meal.

Cats may infrequently develop transient DM. Intact dogs will rarely develop transient DM that resolves when they are neutered. These cats and dogs may go through a period in which they do not require insulin therapy, and insulin therapy may actually be dangerous, leading to potentially fatal hypoglycemia. Therefore, constant monitoring of clinical signs indicative of insulin overdose (weight gain, lethargy, ataxia, confusion, seizures) and continued monitoring by the veterinarian (glucose curves or fructosamine measurement) are needed.

When presenting care recommendations to owners, it is important to present the gold-standard noted above despite the fact that some owners may not be able (or want) to provide this level of care.

DM = diabetes mellitus; NPH = neutral protamine Hagedorn; PZIR = protamine zinc insulin



## Follow-Up

While 0.5 U/kg is a safe starting dose for insulin, it is usually not the dose that the animal is going to require for long-term treatment. The dose is changed based on clinical signs and glucose curves, which are performed approximately every 2 weeks for 1 to 2 months.

### Blood Glucose Curves

- A blood glucose curve is performed by measuring blood glucose concentration every 2 hours for 10 to 12 hours.
- After initial glycemic regulation is achieved (blood glucose should range between 100 and 250 mg/dL for a dog and 100 and 300 mg/dL for a cat), a blood glucose curve is performed every time the owner notices clinical signs consistent with hyperglycemia or hypoglycemia, or when other clinical signs (such as vomiting or signs of lower urinary tract infection) develop.
- If the dog or cat has no clinical problems, a blood glucose curve is performed every 3 to 4 months.

Blood glucose curves and concentrations are always interpreted in view of clinical signs. For example, if a dog is well regulated and has no evidence of polyuria, polydipsia, polyphagia, or weight loss, and blood glucose concentrations range from 180 to 250 mg/dL over a 12-hour period, the dose of insulin does not need to be changed. However, in a dog with the same blood glucose concentrations that has the signs mentioned above, the dose of insulin should be increased.

### Serum Fructosamine Concentration

Occasionally cats will not tolerate a glucose curve and blood glucose measurements will not be reliable due to stress hyperglycemia. In this case, serum fructosamine concentration can be used for patient monitoring.

Fructosamine is formed from a nonenzymatic insulin-independent bond of glucose to various serum proteins. Fructosamine level reflects serum blood glucose concentrations over a 1- to 3-week period. Fructosamine can be elevated when the dose of insulin is too low (**Figure 1**), but it may also be elevated when an insulin dose is too high (**Fig-**

**ure 2**). Therefore, interpretation of fructosamine concentration, as well as glucose curves, must be performed in consideration of the clinical signs.

### Somogyi Effect

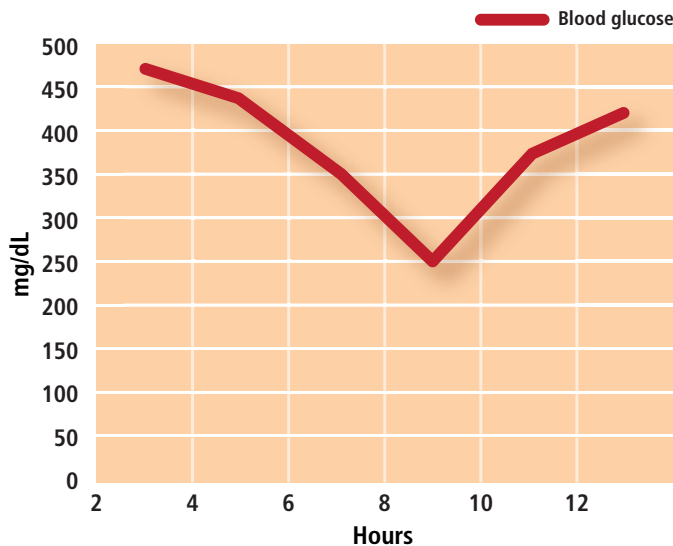
The Somogyi effect occurs when a high dose of insulin causes potentially fatal hypoglycemia; catecholamines (epinephrine and norepinephrine), glucocorticoids, glucagon, and growth hormone are secreted in response to severe insulin-induced hypoglycemia and cause pronounced hyperglycemia.

### Patient Monitoring

In addition to owners monitoring clinical signs, they should also record daily water intake, appetite, insulin dose, glucosuria, and absence of ketonuria. This daily log is brought to the veterinarian at each reexamination. In cats, it may be helpful for the owners to purchase a baby scale and weigh and record the cat's weight once a week.

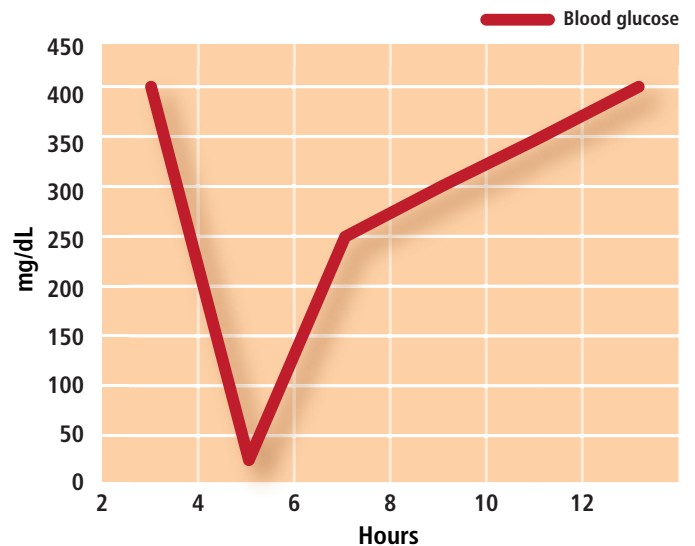
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### 1. Insulin Dose Too Low



High blood glucose levels in a patient in which the insulin dose is too low and fructosamine concentration is high.

### 2. Insulin Dose Too High



The Somogyi effect and high blood glucose levels in a patient in which the insulin dose is too high and fructosamine concentration is high.

**Complications**

**Dogs & Cats**

- Urinary tract infections
- Peripheral neuropathy
- Glomerulopathy<sup>10</sup>

**Dogs**

- Atherosclerosis<sup>11</sup>
- Hypertension
- Cataracts
- Uveitis

**Course**

DM is usually a life-long disease that requires constant adjustment of insulin dose. Cats and dogs may be well regulated for a long time on the same dose of insulin, but will ultimately require adjustments. Concurrent disorders, which develop commonly, complicate the regulation. While the concurrent disorder is untreated, the animal develops insulin resistance and becomes hyperglycemic (Figure 3). Once the concurrent

**Tx at a Glance**

<b>Insulin</b>	Usually given after meals, twice a day at 12 H intervals; starting dose is 0.5 U/kg
<b>Appropriate diet</b>	Fixed amount; fed before insulin administration, twice a day at 12 H intervals
<b>Exercise</b>	Fixed and moderate

disorder is treated effectively, insulin resistance resolves.

**Relative Cost**

- Diagnosis: \$
- Evaluation for presence of concurrent disease at time of diagnosis: \$\$\$\$
- Treatment and follow-up care for uncomplicated cases: \$/visit, 3 to 4 visits/year

**Prognosis**

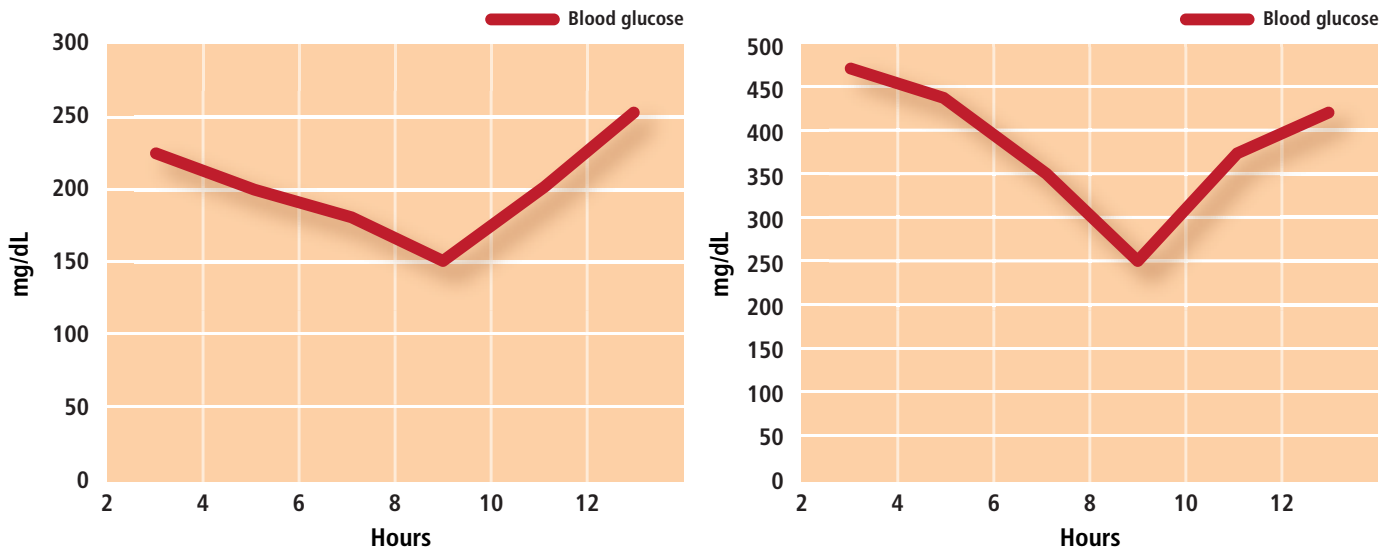
The prognosis for patients with DM is good, as long as the disease is treated and monitored appropriately. This requires significant devotion on the part of the owner and excellent communication between the owner and the veterinarian. ■

**Cost Key**

\$ = < \$100	\$\$\$\$ = \$500–\$1000
\$\$ = \$100–\$250	\$\$\$\$\$ = > \$1000
\$\$\$ = \$250–\$500	

See Aids & Resources, back page, for references, contacts, and appendices. Article archived on [cliniciansbrief.com](http://cliniciansbrief.com)

**3. Insulin Resistance Due To Concurrent Disorder**



Blood glucose curve in a cat receiving 3 units of insulin twice a day before it developed a urinary tract infection (left); blood glucose curve of the same cat with a concurrent urinary tract infection receiving the same dose of insulin twice a day prior to antibiotic therapy (right). It is important to note that, despite hyperglycemia, the dose of insulin should not be increased during antibiotic therapy. Treatment with appropriate antibiotics will result in increased sensitivity to insulin and the dose of 3 units Q 12 H is likely to suffice.

DM = diabetes mellitus