# FELINE DIABETES MELLITUS: ADVANCES IN TREATMENT

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Diabetes mellitus (DM) is one of the most common endocrine diseases affecting 1 in every 200–300 cats; nearly 240,000 cases of feline DM are diagnosed annually.[1] Despite the prevalence of diabetes in the cat population and the increasing frequency of the disease, treatment of diabetic cats is frustrating and often associated with tremendous complications. While insulin therapy and high-fiber diets are the mainstay of DM treatment in cats, many diabetic cats experience complications, such as hypoglycemia and progressive neuropathy, associated with conventional therapy.[2-7] In a recent study, 10% of diabetic cats had documented hypoglycemia caused by an insulin overdose.[6] Obese cats (>6 kg) were much more likely to become hypoglycemic and lack autonomic warning signs of hypoglycemia.[6] Because of the difficulty in achieving adequate glycemic control with insulin therapy in cats, diabetic neuropathy is a common attending condition in diabetic cats. In one study, all diabetic cats suffered from subclinical forms of diabetic neuropathy as evidenced by impaired motor and sensory peripheral nerve conduction.[7]

The latest clinical and histological evidence suggests that type II DM is the most frequently occurring form of DM in cats and humans.[2-4] Type II DM in cats is characterized by an impaired ability to secrete insulin following a glucose stimulus and is caused by both a defect in pancreatic beta cells and peripheral insulin resistance.[2-4] The etiology type II DM is multifactorial with obesity, genetics, diet, and amyloidosis of the islets involved in the development of this form of DM in humans and cats.[2-4] The classic metabolic abnormalities found in type II DM—decreased insulin secretion and peripheral insulin resistance—may be consequences of abnormal amyloid production by pancreatic cells.[2-4] Despite the presence of type II DM in many diabetic cats, the advanced nature of their disease (amyloid deposition, glucose toxicity) often requires that insulin therapy be instituted.[2]

Insulin is often used to treat DM in cats, and dietary fiber may be used to improve diabetic control in cats.[8] In one study, 23 client-owned diabetic cats were fed canned high insoluble fiber or low-fiber diets in a 16-week crossover design and showed improvement on the high-fiber diet.[8] A significant effect of the insoluble fiber diet was found on mean daily caloric intake, mean fasting blood glucose (FBG), and mean glycosylated hemoglobin (GHb).[8] However, this study looked at canned high-fiber diets rather than dry high-fiber diets. The carbohydrate content of dry diets, especially those containing high insoluble fiber, is approximately 36%–40%. In contrast, the canned high-fiber diets are approximately 23% carbohydrate on a dry matter basis.

The cat is an obligate carnivore and as such is unique in its insulin response to dietary carbohydrates, protein, and fat. The feline liver exhibits normal hexokinase activity, but glucokinase activity is virtually absent.[9] Glucokinase converts glucose to glycogen for storage in the liver and is important in "mopping up" excess post-prandial glucose. Normal cats are, in fact, similar to diabetic humans because glucokinase levels drop precipitously with persistent hyperglycemia in humans suffering from type II DM. Amino acids, rather than glucose, signal insulin release in cats.[10] In fact, a recent publication demonstrated more effective assessment of insulin reserve in cats using the arginine response test rather than a glucose-tolerance test.[11] Another unusual aspect of feline metabolism is the increase in hepatic gluconeogenesis seen after a normal meal. Normal cats maintain essential glucose requirements from gluconeogenic precursors (i.e., amino acids) rather than dietary carbohydrates. As a result, cats can maintain normal blood glucose concentrations even when deprived of food for over 72 hours.[10] Feeding has very little effect on blood glucose concentrations in normal cats.[2,12] In summary, the cat is uniquely adapted to a carnivorous diet and is not metabolically adapted to ingestion of excess carbohydrates.

When type II DM occurs in cats, the metabolic adaptations to a carnivorous diet become even more deleterious, leading to severe protein catabolism. Feeding a diet rich in carbohydrates may exacerbate hyperglycemia and protein wasting in these diabetic cats. In fact, in humans with type II DM, the first recommendation is to restrict excess dietary carbohydrates such as potatoes and bread and to control obesity by caloric restriction.[13] Furthermore, humans with type II DM have been shown to have improved glycemic control and improvement in nitrogen turnover during weight loss when a low-energy diet (high protein) was combined with oral hypoglycemic therapy.[14]

A low-carbohydrate, high-protein diet, which is similar to a cat's natural diet (mice), may ameliorate some of the abnormalities associated with DM in the cat. Initial studies using a canned high-protein/low-carbohydrate diet and the starch blocker acarbose have shown that 58% of cats have their insulin injections discontinued, and those with continued insulin requirements could be regulated on a much lower dosage (1U b.i.d.).[15] Comparison of canned high-fiber vs. low-carbohydrate diets showed that cats fed low-carbohydrate diets were 10 times more likely to have their insulin injections discontinued.[16] The diet formulation is critical in that most dry cat food formulations contain excessive carbohydrates; therefore, canned cat foods and preferably high-protein or kitten formulations should be used for initial treatment of diabetic cats. Cats should be fed no more than 30 kcal/lb of ideal body weight in 2 equal meals per day. Caution should be used when initially changing from dry to canned foods, as insulin requirements may decrease dramatically; a reduction in insulin dosage may be required.

## TREATMENT OF FELINE DM WITH ORAL HYPOGLYCEMICS

Treatment of type II DM is aimed at attenuating the physiologic abnormalities by decreasing hepatic glucose output and glucose absorption from the intestine, increasing peripheral insulin sensitivity, and increasing insulin secretion from the pancreas. In cats, the clinician must rely on the response to oral hypoglycemic agents as a guide to whether the cat has sufficient beta-cell function to be managed with oral hypoglycemic agents. Oral hypoglycemic agents include the sulfonylureas (glipizide, glyburide, glimiperide), biguanides (metformin), thiazolidinediones (troglitazone), alpha-glucosidase inhibitors (acarbose), and transition metals (chromium, vanadium).[17] Indications for oral hypoglycemic therapy in cats include normal or increased body weight, lack of ketones, probable type II diabetics with no underlying disease (pancreatitis, pancreatic tumor), history of diabetogenic medications, and willingness of the owners to administer oral medication rather than an injection. Reversal of glucose toxicity using a short course of insulin therapy prior to or in combination with oral hypoglycemic agents may improve the response to oral hypoglycemic agents. For optimal response, diet should consist of low-carbohydrate/high-protein canned foods only.

The alpha-glucosidase inhibitors impair glucose absorption from the intestine by decreasing fiber digestion and hence glucose production from food sources.[18] Acarbose is used as initial therapy in obese, pre-diabetic patients suffering from insulin resistance or as adjunct therapy with sulfonylureas or biguanides to enhance the hypoglycemic effect in patients with DM. Side effects include flatulence, loose stool, and diarrhea at high dosages. One advantage of these medications is that they are not absorbed systemically and may be used in conjunction with other oral hypoglycemics or insulin. They are not indicated in patients with low body weight because of their effects on nutrition. The author has had experience with acarbose at a dosage of 12.5 mg/cat b.i.d. with meals; side effects, although rare if diet is adjusted, include semi-formed stools or, in some cases, overt diarrhea. Acarbose is an excellent agent when combined with insulin to improve glycemic control. Cats given acarbose will respond to a lower dosage of insulin, and hypoglycemic episodes can be reduced.

The mechanism of action of the sulfonylureas is to increase insulin secretion and improve insulin resistance.[17] In cats, glipizide has been used to successfully treat DM at a dosage of 5 mg b.i.d. The patient is evaluated weekly or every 4 weeks for a period of 2–3 months. If serum fructosamine decreases to <400 micromol/L, glipizide should be continued at the same dosage and the cat reevaluated in 3–6 months. If the serum fructosamine remains greater than 400 micromol/L after 2–3 months of therapy and the cat is still symptomatic (PU/PD, weight loss), glipizide should be discontinued and insulin therapy or combination insulin/oral hypoglycemic therapy instituted. If the serum fructosamine remains greater than 400 micromol/L and the cat becomes

asymptomatic, the glipizide should be continued indefinitely and the cat rechecked in 3–6 months. Side effects of oral hypoglycemics include severe hypoglycemia (rare in cats), cholestatic hepatitis, and vomiting. Gastrointestinal side effects, which occur in about 15% of cats treated with glipizide, resolve when the drug is administered with food.[19]

## INSULIN THERAPY

Although mammalian insulins are structurally similar, small differences in amino acid sequences may be found between species. Mammalian insulin is composed of 51 amino acids arranged in 2 polypeptide chains.[20] The A chain contains 21 amino acids, and the B chain contains 30 amino acids.[20] Pork insulin is most similar to human insulin in structure differing by only 1 amino acid in the B chain. Human recombinant insulin is the most available insulin preparation on the market and is perfectly acceptable as insulin therapy for all dogs and most cats. Human insulin is commonly used in small animals and can be formulated as short acting (Humulin® R [regular]), intermediate acting (Humulin® L [Lente], Humulin® N [NPH]) or long acting (Humulin® U [Ultralente]). Eli Lilly markets human insulin under the brand name of Humulin®; Novo Nordisk manufactures human recombinant insulin under the name of Novolin®. Beef insulin is available as a U-40 protamine zinc insulin (PZI) from Blue Ridge Pharmaceuticals.

### Insulin Duration

Insulin preparations may be short acting (regular insulin), intermediate acting (Lente, NPH), or long acting (Ultralente, PZI). The portion of the insulin that prolongs absorption from the subcutaneous tissue is different for the 2 types of extended-duration insulin. For NPH and PZI insulins, protamine is added in increasing concentrations to retard insulin absorption.[21] In the case of lente insulins, the absorption of insulin is controlled by the size of the zinc-insulin crystals. Semilente, which is no longer manufactured, is composed of small zinc-insulin crystals. Ultralente or extended insulin-zinc preparation, on the other hand, is composed of large zinc-insulin crystals that are more slowly absorbed.[21] Lente insulin is a mixture of 30% prompt zinc-insulin suspension and 70% extended insulin zinc.[21] Because of the small zinc-insulin crystal component, lente insulin appears to improve postprandial hyperglycemia.[22]

### Insulin Concentration and Syringes

Insulin is commercially available in 40, 100, and 500 U/ml concentrations designated U-40, U-100, and U-500, respectively. One unit of insulin is approximately equivalent to 36 µg. In the United States, U-100 insulin is the primary insulin concentration available. Blue Ridge Pharmaceuticals is the sole manufacturer of U-40 insulin (PZI) in the United States. Regardless of the concentration of insulin used for therapy, it is absolutely essential that owners purchase the appropriate syringe for the concentration of insulin. There are 4 different types of insulin syringes available: U-100 insulin syringes are manufactured as low-dose (0.3-ml, 0.5-ml) and 1-ml capacities; U-40 syringes are only available as 1-ml capacity. All insulin syringes are packaged with a fine 26- or 27-gauge injection needle.

### Insulin Dosage

Initial insulin therapy in the uncomplicated diabetic should be designed to mimic physiologic insulin concentrations without induction of hypoglycemia. Initial insulin therapy should be conservative, followed by incremental increases in insulin dosage based on resolution of clinical signs, urine glucose monitoring, and serial blood glucose curves. In dogs, intermediate-acting insulin is administered twice daily at a starting dosage of 0.4–0.5 U/kg. In cats, initial insulin dosages range from 0.2–0.5 U/kg.[23] Cats should be given twice-daily insulin therapy because of rapid metabolism of insulin. Most authors recommend using twice-daily ultralente, although this author has had success using twice-daily lente or NPH insulin in cats. If PZI is used, a dosage of 1–3 units per cat is often recommended as once- or twice-daily therapy.

### Insulin Injection Location and Technique

The site of insulin injection should be discussed with the pet owner. Absorption of insulin from various injection sites in the body may differ.[24] In animals, the back of the neck, or scruff, has commonly been used as a site for insulin injection. However, this site has several disadvantages because of lack of blood flow and increased fibrosis caused by repeated injections. The author recommends administration of insulin at sites along the lateral abdomen and thorax. The owner should rotate the site of injection each day, as repeated insulin injections in the

same site may lead to adipose atrophy. Many commercially available pamphlets outline injection techniques, feeding, hypoglycemic episode management, and provide a formatted log sheet for owners to record food intake, clinical signs, urine glucose measurements, and insulin dosages.

## MONITORING FELINE DM

### Clinical Signs

Although often overlooked, clinical signs such as polydipsia or polyuria are the best indicators of adequate diabetic regulation. Under-regulation is often manifested as continued or worsening polydipsia, polyuria, weight loss, vomiting, diarrhea, anorexia, neuropathy in cats, and cataracts in dogs. Over-regulation is often signaled by weight gain (as a result of the anabolic effects of insulin) and signs of hypoglycemia such as weakness or coma. Body weight should remain stable or normalize with underweight animals gaining weight and overweight animals losing weight. Irritability or changes in personality (aggressiveness, biting) should alert the clinician to a worsening diabetic situation in a cat. Signs of ketosis include vomiting, diarrhea, weakness, and acetone odor to the breath in both dogs and cats. Hyperosmolar or mixed ketotic-hyperosmolar syndrome in cats may manifest as weakness, severe dehydration, bradycardia, hypotension, and eventually coma.[25]

### Urine Glucose Monitoring

Urine glucose is a measure of trends in blood glucose and can be used to alert the owner to hypoglycemia. Urine glucose monitoring may be performed at home by the owner, is not affected by stress, and may indicate insulin-induced hyperglycemia (Somogyi effect). Urine glucose should decrease to trace or 1+ with appropriate therapy. Consistently negative urine glucose readings indicate a need to decrease or discontinue insulin therapy in diabetic cats. Consistently high urine glucose indicates the need for blood glucose evaluation. Glucotest™ (Purina Veterinary Diagnostics) is a new urinary glucose monitoring "confetti" that may be sprinkled into cat litter to facilitate urine glucose testing. Clients are instructed to monitor urine glucose on a daily basis following any change in insulin regimen or diet.

### Glucose Monitors

Glucose monitors designed for home monitoring in humans are inexpensive, accurate, rapid, and require only a drop of blood. Although reasonably accurate in the blood glucose range of 80–250 mg/dl, these glucose monitors are designed to read 10–20 mg/dl lower than the actual value as glucose approaches the hypoglycemic range (<80 mg/dl). Factors that affect accuracy of these monitors include altitude, oxygen therapy, patient hematocrit, shock, dehydration, severe infection, post-prandial state, and out-of-date or improperly stored test strips. Whole blood glucose concentrations are lower than serum glucose and the manufacturer should be consulted about the suitability of these monitors for feline patients. The blood glucose curve is found by taking an initial blood sample and having the owner feed the same amount and type of food. The client should administer insulin, allowing assessment of the injection technique. Blood samples are then collected at 2-hour intervals for a period of 12 hours in most cases.

### Ideal Blood Glucose Curve

The ideal blood glucose curve is characterized by 3 features (Figure 1). The ideal glucose curve has a glucose nadir (lowest blood glucose concentration on the curve) between 100–150 mg/dl in cats and 80–120 mg/dl in dogs. The time of the glucose nadir indicates peak insulin action. The nadir should occur approximately halfway through the dosing interval. For example, if insulin is being given every 12 hours, the nadir should fall 5–6 hours after the dose. The glucose differential is the difference between the glucose nadir and the blood glucose concentration prior to the next insulin dose. The glucose differential should be less than 150 mg/dl in cats. The ideal

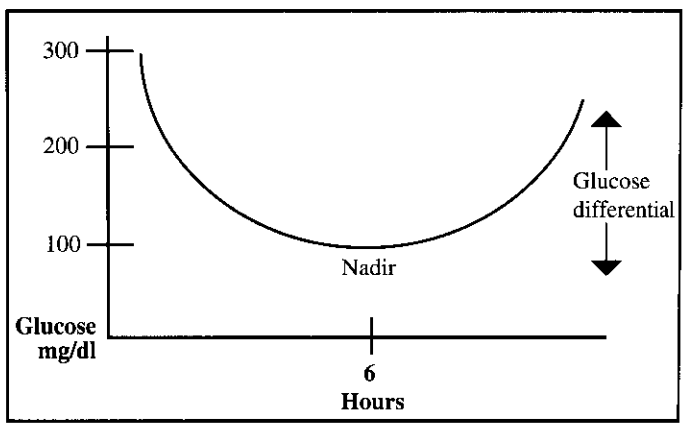


**Figure 1.** Ideal blood glucose curve.

glucose curve in a cat receiving b.i.d. insulin injections starts at 250 mg/dl with a nadir of 100 mg/dl and a return to 250 mg/dl 12 hours later. The ideal glucose curve in a dog starts at 200 mg/dl with a nadir of 80 mg/dl and a return to 200 mg/dl 12 hours later.

The duration of insulin action is related to both the time of the glucose nadir and the absolute concentration of the glucose nadir. One cannot make a determination of insulin duration unless the target glucose nadir concentration (80–150 mg/dl) has been achieved. If the glucose nadir occurs approximately halfway through the dosing interval, the duration of action of insulin should be adequate.

**Problems Identified on the Blood Glucose Curve**

It is very rare to obtain a perfect glucose curve in a single patient or even a repeatable curve in the same patient over time. Generally, blood glucose curve problems can be differentiated by the characteristics of the curve and the insulin dosage (per dosing interval). If the patient is receiving >2.2 U/kg of insulin per dose, insulin resistance should be investigated. Causes of insulin resistance in cats include hyperthyroidism, hyperadrenocorticism, acromegaly, estrus, drug therapy, and concurrent infections (especially urinary). If the animal is receiving <2.2 U/kg per dose, the blood glucose curve will usually be indicative of one of the following: insufficient dosage of insulin, short duration of action of insulin, insulin-induced hypoglycemic hyperglycemia (Somogyi effect), insulin overlap, or prolonged insulin action. Corrective actions include increasing the insulin dose, changing to a longer-acting insulin or twice-daily insulin regimen, reduction of the insulin dose by 25%, or changing to a shorter duration or mixture of insulin (30% regular, 70% NPH), respectively.

**Monitoring Using Glycosylated Serum Proteins ($Hb_{A1c}$, fructosamine)**

Methods of assessing long-term glycemic control are better indicators of response to therapy with oral hypoglycemics than are spot glucose determinations or blood glucose curves. The author prefers to monitor resolution of clinical signs of DM, such as polydipsia and polyuria, serum fructosamine concentrations, and midday blood glucose concentrations rather than serial glucose curves in cats undergoing both insulin and oral hypoglycemic therapy.[26] Baseline serum fructosamine concentrations should be collected for every diabetic cat or dog. With either insulin or oral hypoglycemic therapy, serum fructosamine concentrations should decrease to less than 450 micromol/L. Serum fructosamine concentrations less than 400 micromol/L indicate excellent control (Figure 2). It is often helpful to interpret the serum fructosamine in concert with a midday blood glucose concentration. In fact, the author collects a serum chemistry profile to evaluate blood glucose, liver enzymes, blood urea nitrogen, creatinine, electrolytes, acid-base status, and serum fructosamine. Midday blood glucose concentrations should be less than 180 mg/dl in cats with well-controlled diabetes. Figure 2 is an algorithm for interpretation of the serum fructosamine and midday blood glucose values.

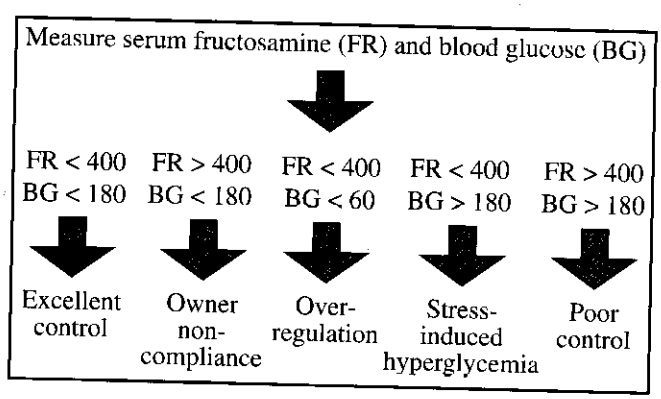


**Figure 2.** Algorithm for monitoring serum fructosamine in diabetic cats.

Glycosylated hemoglobin is a measure of the mean blood glucose concentration over the past 70 days (red blood cell lifespan in cats). Glycosylated hemoglobin is more difficult to measure in cats than in dogs or humans, and it may take more than a week for the laboratory to return results. Values for glycosylated hemoglobin in normal cats are low (1.5%–2%) compared with humans (6%–8%) or dogs, and there is considerable overlap in normal vs. diabetic cats. Therefore, the author does not use this parameter to monitor diabetic cats.

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