# T35
# Treatment of Diabetes Mellitus in Dogs and Cats

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## INSULIN

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 two polypeptide chains.[1] The A-chain contains 21 amino acids and the B chain contains 30 amino acids.[1] Pork insulin is most similar to human insulin in structure differing by only one amino acid in the B chain. Human recombinant insulin is preferred for human diabetic patients especially in those individuals that are prone to develop allergies or immune resistance to animal-source insulin.[2] 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)), or intermediate-acting (Humulin L (Lente), Humulin N (NPH)). Eli Lilly markets human insulin under the brand name of Humulin; Novo Nordisk manufactures human recombinant insulin under the name of Novolin. Novolin can be purchased as Novolin R (Regular), Novolin L (Lente), Novolin N (NPH), or as a mixture of NPH and regular insulin (Novolin 70/30).

Animal-source (e.g., beef, pork and beef-pork) insulin has previously been the most common insulin preparation used in veterinary medicine. However, with the development of genetically engineered recombinant human insulin, animal-source insulins have fallen out of favor in human medicine. As a result of the advantages of human recombinant insulin for treatment of diabetes in humans, both Eli Lilly and Novo Nordisk have recently discontinued many of their animal-source insulin preparations.[3] Lilly has also discontinued human Lente and Ultralente insulin. Synthetic insulins which are ultra-short or ultra-long acting have been developed for use in human medicine. Preliminary studies on glargine (Lantus) have shown that it has advantages over PZI insulin for cats.

Beef insulin is most similar to cat insulin differing by only one amino acid in the A chain. If a change in insulin source is contemplated, one should realize that different types and brands of insulin have different pharmacologic properties. Pork insulin is identical to dog insulin therefore, the new pork Lente insulin should be the best choice for dogs.

## INSULIN DURATION

Insulin preparations may be short-acting (regular insulin), intermediate (Lente, NPH) or long-acting (Ultralente, PZI). The portion of the insulin that prolongs absorption from the subcutaneous tissues is different for the two types of extended duration insulin. For NPH and PZI insulin, protamine is added in increasing concentrations to retard insulin absorption.[5] Intermediate duration insulin, such as NPH, are commonly used as twice daily therapy in dogs. However, NPH may not last long enough in some cats even with twice daily therapy. 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 which has also been discontinued, on the other hand, is composed of large zinc-insulin crystals which are more slowly absorbed.[5] Lente insulin is a mixture of 30% prompt zinc-insulin suspension and 70% extended insulin zinc.[5] Lente insulin, because of the small zinc-insulin crystal component, appears to improve postprandial hyperglycemia.[6]

The nomenclature for insulin duration is relatively straightforward. Regular insulins are usually named by the species source (Humulin, Ilentin I (beef-pork)) followed by the initial R or the word "Regular". Lente insulins are named by the species of origin (Humulin) and by the initial L or the word "Lente". NPH insulin is named by species of origin and the letter N or the initials NPH. Ultralente insulins are described by the letter U or the word "Ultralente".[7]

### Insulin Concentration

Insulin is commercially available in 40, 100, and 500 U/ml concentrations which are designated U-40, U-100, and U-500 respectively.[8] One unit of insulin is approximately equivalent to 36 ug.[9,10] For small animals on low dosages of insulin, U-40 insulin offers an advantage over U-100 insulin because a small dose can be more easily measured. Regardless of the concentration of insulin used for therapy, it is absolutely essential that owners purchase the appropriate syringe for the concentration of insulin.[9]

### Insulin Syringes

In general, there are four 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. [9,10] All insulin syringes are packaged with a fine 26 or 27 gauge injection needle. In cats and small dogs (<10 kg), the use of low-dose (0.3 or 0.5 ml) syringe is recommended.

### 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, the starting insulin dose is 0.4–0.7 U/kg once or twice daily. Intermediate acting insulin tends to be more bioavailable and therefore, more potent and is most appropriately dosed at the lower end of the range. Therefore, if intermediate acting insulin is administered twice daily, a starting dosage of 0.4–0.5 U/kg is appropriate for most dogs. On the other hand, long acting insulins such as PZI, are dosed at the higher end of the dosage range as they are absorbed more slowly, tend to be less potent, and are administered once daily. In cats, initial insulin dosages range from 0.2–0.5 U/kg.[10] If intermediate acting insulin is used, it must be administered twice daily because of the short duration of action in cats.

### Insulin Injection Location and Technique

The site of insulin injection should be discussed with the pet owner. Absorption of insulin from various injections sites in the body may differ.[11] 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 at this site. The author recommends administration of insulin at sites along the lateral abdomen and thorax. The owner should rotate the site of injection each day. 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.

### Summary of Insulin for Cats and Dogs

Cats: Administer human recombinant glargine insulin twice daily initially. Starting dose (1–2 U/cat BID). Use an ultra low-carbohydrate diet (ex: Purina DM canned) to facilitate insulin action. Rand *et al* reported remission rates greater than 90% in newly diagnosed diabetic cats using this regimen.

Dogs: Administer human or pork Lente insulin twice daily. Starting dose (0.5 U/kg SQ BID). Use a high fiber, low fat diet to facilitate insulin action.

### Diet and Exercise

The goals of dietary therapy in diabetes mellitus for both cats and dogs are to provide sufficient calories to maintain ideal body weight and correct obesity or emaciation, to minimize post-prandial hyperglycemia, and to facilitate ideal absorption of glucose by timing meals to coincide with insulin administration. Caloric intake should be 60–70 Kcal/kg/day for smaller dogs and 50–60 Kcal/kg/day for larger dogs. Obese animals should have their body weight reduced gradually over a period of 2–4 months by feeding 60–70% of the calculated caloric requirements for ideal body weight. Underweight animals should be fed a high-caloric density food based on caloric intake for optimum body weight. Once ideal body weight is reached, the animal may be switched to a high fiber diet. Table 2 lists the fiber and

caloric content of some commercially available dog foods. The feeding schedule should be adjusted to the insulin therapy.

Micronutrients may be added to the diet to improve glucose control in some dogs. Compounds containing the transition metals, vanadium and chromium, have been shown to have insulinomimetic properties when administered to diabetic rodents. A recent USDA study of 180 human patients with NIDDM found that administration of 1,000 μg of chromium picolinate once daily resulted in amelioration of the classic signs of diabetes and normalization of blood levels of hemoglobin A1c. Current research indicates that transition metals bypass the insulin-receptor and activate glucose metabolism within the cell. Unlike insulin, vanadium and chromium do not lower blood glucose concentrations in normal animals.

One of the newer approaches to managing diabetes mellitus in dogs combines the use of starch blends, such as carboxymethyl cellulose and fermentable fibers. Barley and sorghum may be used to blunt the post-prandial rise in blood glucose, adjust postprandial insulin to appropriate levels, and to help blunt glucose surge. Fermentable fibers, such as FOS, beet pulp and gum arabic, increase short chain fatty acids from the large intestine which in turn increases glucagon like peptide-1 secretion and activity. GLP-1 is necessary for normal insulin secretion and for normal timing of insulin secretion after eating.

### EXERCISE

Exercise should be kept constant in diabetic animals. The owners should be instructed to walk the animal daily and avoid intermittent episodes of strenuous exercise, such as racing or hiking. Increasing exercise in obese diabetic animals will reduce insulin resistance and improve glycemic control.

### HYPOGLYCEMIA

Clinical signs of hypoglycemia in diabetics are initially consistent with epinephrine release to counter the hypoglycemia. Nervousness, anxiety, vocalization, muscle tremors, ataxia, and pupillary dilatation should alert the owner to the possibility of hypoglycemia. At this point, the animal should be offered food and the owner should seek veterinary advice. Late in the course of hypoglycemic shock the animal may become recumbent, comatose or seizure. If access to a vein is not readily available or if the owner is administering therapy, 50% dextrose (Karo syrup, pancake syrup) may be applied to the mucous membranes of the mouth using a large syringe. One should caution the owner to pour the syrup on the gums from a reasonable distance from the animal's teeth to prevent accidental injury from biting. The owner should transport the animal to a veterinarian as soon as possible. At the veterinary office, treatment should consist of administration of a slow IV bolus of 50% dextrose (0.5 g/kg diluted 1:4). Thereafter in animals suffering from hypoglycemia of any cause, a continuous infusion of 5% dextrose should be administered until the animal can be fed. Many animals that experience insulin overdose will suffer cerebral edema and temporary blindness or behavior changes; often these signs are temporary and resolve after several weeks or months.

**Table 2. Macronutrient content of selected dog foods.**

| Diet | Food form | % Nutrient dry matter | | | |
|---|---|---|---|---|---|
| | | Protein | CHO | Fat | Fiber |
| Prescription diet r/d | Can | 26 | 36 | 7 | 21 |
| Prescription diet r/d | Dry | 25 | 39 | 7 | 22 |
| Prescription diet w/d | Can | 16 | 56 | 12 | 13 |
| Prescription diet w/d | Dry | 17 | 54 | 7 | 16 |
| Purina DCO-formula | Dry | 23 | 43 | 11 | 7 |
| Fit N Trim | Dry | 17 | 61 | 9 | 9 |
| Cycle 3 light | Can | 19 | 53 | 9 | 5 |

## DIET: CATS

The cat is an obligate carnivore and 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 human beings suffering from type 2 diabetes mellitus. Amino acids, rather than glucose, are the signal for 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 from dietary carbohydrates. As a result, cats can maintain normal blood glucose concentrations even when deprived of food for over 72 hrs.[10] Feeding has very little effect on post-prandial glucose concentrations in normal or diabetic cats; instead, cats increase lactate absorption from the colon and increase glucose 6 hours post-meal.[2,12] In summary, the cat is uniquely adapted to a carnivorous diet and is not metabolically adapted to ingestion of excess carbohydrate.

When type 2 diabetes 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 human beings with type 2 diabetes, the first recommendation is to restrict excess dietary carbohydrates, such as potatoes and bread, and to control obesity by caloric restriction.[13] Furthermore, human beings with type 2 diabetes mellitus 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 in fact to a cat's natural diet (mice), may ameliorate some of the abnormalities associated with diabetes mellitus in the cat. Initial studies using a canned high protein/low carbohydrate diet and the starch blocker acarbose have shown that 58% of cats discontinue insulin injections and those with continued insulin requirements could be regulated on a much lower dosage (1U BID).[15] Comparison of **canned** high fiber vs. low carbohydrate diets showed that cats fed low carbohydrate diets were 4 times more likely to discontinue insulin injections.[16] The most recent data from that study indicates that approximately 70% of cats can discontinue insulin injections when fed a restricted carbohydrate diet! The diet formulation is critical in that most dry cat food formulations contain excessive carbohydrates; therefore, **canned** cat foods and preferably high protein 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 two 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. **Any canned cat food product usually contains < 10% carbohydrates on a DMB (exception rice products and those with sauces containing cornstarch) therefore, when in doubt use a canned product rather than a specific brand.** Examples of canned diets low in carbohydrates include Purina DM, Friskies, and Fancy feast. The most restricted carbohydrate dry formulation is Purina DM dry.

## ORAL HYPOGLYCEMICS: CATS ONLY

Treatment of type 2 diabetes mellitus 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 owners willingness 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 diabetes mellitus. 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 of low body weight because of their effects on nutrition. The author has had experience with acarbose at a dosage of 12.5 mg/cat BID with meals; side effects, although rare if diet is adjusted, include semi-formed stool 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.[15]

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 diabetes mellitus at a dosage of 5 mg BID. 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 micromol/L after 2–3 months of therapy and the cat is still symptomatic (PU/PD, wt. loss), glipizide should be discontinued and insulin therapy or combination insulin/oral hypoglycemic therapy should be instituted. If the serum fructosamine remains greater than 400 micromol/L and the cat becomes asymptomatic, the glipizide should be continued indefinitely and the cats should be 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]

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