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### **Canine and Feline Diabetes Mellitus I**

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#### **PATHOPHYSIOLOGY OF DM**

Diabetes mellitus (DM) is a common endocrine disease in dogs and cats characterized by an absolute or relative deficiency of insulin. This results in a decreased ability of cells to take up and utilize not only glucose, but also amino acids, fatty acids, and electrolytes. In addition the lack of insulin results in increased gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, and protein catabolism. Factors that have been identified as predisposing factors in cats include obesity, advancing age and being male. In dogs, older females are at higher risk of developing DM. Poodles, Dachshunds, Miniature Pinschers, Beagles, Golden Retrievers, and Miniature Schnauzers are considered to be at higher risk than the general canine population. Keeshonden appear to have a genetic predisposition to the disease.

Two types of DM are recognized in man, and these classifications can be applied to the disease in dogs and cats. Type I DM (insulin dependent diabetes mellitus) is due to an absolute deficiency of insulin. This form of diabetes is characterized by minimal secretory response to  $\beta$ -cell secretagogues such as glucagon, and is the most common form of diabetes recognized in the dog. Type II DM (non insulin dependent diabetes) is characterized by abnormal insulin secretion and peripheral insulin resistance, and results in a stable reregulation of the blood glucose concentration at a higher concentration. This type of DM is rare in the dog but is common in the diabetic cat. The two types of diabetes are classically distinguished by characteristic responses to challenge by insulin secretagogues such as glucose, glucagon, or arginine. In type I DM, there is a decreased or negligible secretion of insulin compared to normal animals, whereas in Type II DM, total insulin secretion may be normal or increased, although the pattern of secretion may be abnormal. The insulin concentration is still insufficient however, to prevent hyperglycemia. The phenomenon of glucose toxicity complicates interpretation of glucagon tolerance tests, particularly in cats, and the glucagon tolerance test is of little practical utility in clinical practice.

#### **DIAGNOSIS**

The diagnosis of DM is made based on characteristic clinical signs of diabetes mellitus (polyuria, polydipsia, polyphagia, and weight loss), and documentation of hyperglycemia and glycosuria. In dogs the diagnosis is usually straight forward, however in cats it may be complicated by the occurrence of marked stress hyperglycemia. When making a diagnosis of DM in cats, it is therefore important not only to document **persistent** hyperglycemia and glucosuria, but also to rule out other diseases that may cause similar clinical signs. Measurement of fructosamine concentrations or urine glucose of samples collected in the home environment may allow the clinician to distinguish between stress induced hyperglycemia (and resultant glycosuria) and persistent hyperglycemia due to diabetes mellitus. Glucosuria may also occur secondary to ketamine anesthesia, chronic renal failure, and post-obstructive diuresis so is not on its own diagnostic for diabetes mellitus. The presence of significant ketonuria together with hyperglycemia, is diagnostic for diabetes mellitus in both dogs and cats.

Cats are also unique in that DM in this species may be transient or intermittent. In one study, 10 diabetic cats were reported to go into spontaneous remission after 1-3 months of therapy. In other studies, up to 70 % of cats with DM were reported to go into spontaneous clinical remission, with good glycemic control. Unfortunately, the glucagon tolerance test is not useful in predicting whether or not a cat is likely to go into remission. In dogs, diabetes mellitus is usually permanent, unless DM occurs secondary to profound insulin resistance, due to hormones such as progestagens and glucocorticoids. This type of diabetes is sometimes referred to as type III DM. In these cases, if the diagnosis is made early and the cause of insulin resistance can be removed, the diabetes may also resolve.

## INSULIN THERAPY

### Classification of Insulin

It is very important for clinicians prescribing insulin to understand the various methods by which they are classified. Insulins may be classified by insulin source, insulin formulation, or duration of action of insulin. Not all forms of insulin are currently commercially available and product availability is likely to continue to change. Insulin formulations that have been available historically include short duration regular insulin (designated R), moderate duration NPH insulin (designated N), moderate duration Lente insulin (designated L), Long duration Ultralente insulin (designated U), and Long duration PZI insulin. Insulins may be derived from bovine, porcine, or human recombinant sources and the concentration may be either 100 units/ml or 40 units/ml. A number of human recombinant insulin analogues are also available.

The types of insulin recommended for use in dogs and cats has been complicated by the recent disappearance of many insulin products from the market. The insulin products that are currently available in the US are listed below:

Insulin products currently available and recommended for use in dogs and cats

- Short acting:
  - **Regular insulin** (Zinc insulin crystals)
    - **Products: Humulin R** [Lilly], **Novolin R** [NovoNordisk] Both human recombinant. 100 U/ml
- Moderate acting:
  - **NPH insulin** (neutral protamine Hagedorn)
    - Complexed with protamine zinc in phosphate buffer
    - **Products: (Humulin N** [Lilly] , **Novolin N** [NovoNordisk] Both human recombinant 100 U/ml
  - **Lente insulin** (3 percent Semilente, seventy percent Ultralente)
    - Mix of crystalline and amorphous crystals in zinc acetate buffer
    - **Products: Vetsulin** [Intervet] Pure pork insulin (40 U/ml)
- Long acting:
  - **PZI insulin**
    - Insulin complexed with protamine and zinc.
    - **Products: PZI Vet**, [Idexx] 90% Beef, 10% Pork (40 U/ml)
  - **Glargine insulin**
    - Insulin analogue
    - **Products: Lantus** [Sanofi-Aventis] , human recombinant (100 U/ml)
  - **Ultralente insulin:** no longer commercially available.

### Insulin Therapy in Cats

Insulin products that are suitable for use in cats include PZI, Glargine and Lente insulins. PZI Vet in one study was effective in achieving glycemic control in 90% of diabetic cats. This insulin is my first choice for use in cats, however it is expensive (\$82/vial, 20c/unit). Preliminary studies of a long acting insulin analogue (insulin Glargine®) have been very promising and this is my second choice insulin in cats. Pork Lente insulin (Vetsulin) may also be used successfully in cats and would be my third choice product. NPH insulin may also be used in the cat although it tends to have a very short duration of action.

The starting dose for insulin in a new feline diabetic patient is 0.25–0.5 Unit/kg or 1–3 U/cat. It is recommended that PZI and Glargine insulins are started at the lower end of this dose.

It is difficult to predict in advance which cats will do better with which insulin formulation. There is some evidence that longer acting insulins are more likely to induce diabetic remission in cats so longer acting insulins are a good first choice in cats. Cats should be carefully monitored for occurrence of hypoglycemia, because of the possibility of remission of diabetes mellitus in the cat. A blood glucose curve (5–14 days) should be performed after making any change in insulin formulation. As a rule shorter acting insulins are more potent than longer acting insulins, so may be more appropriate in cast with

underlying diseases that cause insulin resistance or make cats prone to developing ketosis. Whichever formulation is chosen, twice a day insulin therapy is more likely to result in good glycemic control than one a day therapy. If twice a day treatment is not possible, once a day therapy with PZI Vet or Glargine can result in effective control of clinical signs in some cats. Once a day therapy does increase the risk of hypoglycemia.

### **Insulin Therapy in Dogs**

Insulin formulations that are the most effective in dogs include human recombinant NPH (Humulin N) or Lente (Veterinulin®) insulin at a starting dose of 0.5 U/kg twice a day. Use of human recombinant insulin or pure pork insulin appear to avoid the complications that can occur due to development of anti-insulin antibodies in dogs treated with beef/pork insulin. Long acting insulins such as PZI and Glargine are quite unpredictable in dogs and are not appropriate for the management of most diabetic dogs.

### **Switching From One Insulin Product to Another**

1. Evaluate how well regulated the animal is on current insulin product.
2. Determine potency of new insulin versus old insulin (long acting insulins are less potent than moderate acting insulins).
3. Determine frequency of new insulin administration.
4. Determine new dose based on these factors: If animal has good glycemic regulation or if you are switching to a more potent insulin or increasing the frequency of administration decrease dose by 10–15%, if animal is not tightly regulated and potency of insulin is the same or less keep the same dose. Larger dose adjustments may be needed with changes in frequency of insulin administration.
5. Educate owners about obtaining and using U40 insulin syringes if you are switching to Vetsulin or PZI Vet. It is **NOT** recommended to use U100 syringes with U40 insulin by making a dose adjustment may lead to serious errors. Educate owners about the clinical signs of hypo and hyperglycemia. Make sure they know how to treat an episode of hypoglycemia.
6. Evaluate response to new insulin by evaluation of clinical signs and by performing a blood glucose curve 5–7 days after making the product change. Increase or decrease dose in appropriate increments for the size of the dog or cat.

### **DIETARY MANAGEMENT**

Dietary management should be instituted at the same time as insulin therapy in the diabetic patient. The goal of dietary therapy is to minimize postprandial fluctuations in blood glucose and to potentiate the action of insulin. There are 5 dietary variables that are important in the diabetic patient; diet composition, fiber content, consistency, caloric intake, and feeding schedule.

Studies support the feeding of a high complex carbohydrate (> 50% dry matter), high fiber diet (> 10% dry matter) to dogs with DM. Diets containing increased amounts of soluble fiber (fruits, legumes, oats) delay gastric emptying, alter intestinal transit time and potentiate the actions of insulin in tissues. Increased amounts of insoluble fiber (cellulose, vegetables, grains) alter intestinal transit time and slow starch hydrolysis. The net effect of a high fiber diet is to slow glucose absorption from the intestinal tract, reduce postprandial fluctuations in blood glucose and enhance glycemic control of the diabetic patient. Reduced fat diets are probably appropriate in diabetic patients due to their susceptibility to hepatic lipodosis, pancreatitis and hypercholesterolemia. Research suggests that high fiber diets may also improve glycemic control in cats however other empirical clinical data suggests that feeding a low carbohydrate diet is preferable in diabetic cats (carnivore connection theory), and may improve glycemic control. Some researchers believe that use of such a diet in conjunction with good glycemic control may ultimately result in discontinuation of insulin therapy in the majority of cats. A prospective study comparing a low carbohydrate-low fiber diet to a moderate carbohydrate-high fiber diet in 63 diabetic cats showed improvements in glycemic control in both groups, but there was a higher rate of remission of diabetes mellitus in the low carbohydrate-low fiber diet. These findings support the clinical opinion that low carbohydrate diets in conjunction with good glycemic control increase the likelihood of diabetic remission. If diabetic remission occurs in cats it is most commonly in the first few months of treatment.

Currently I recommend starting with a low carbohydrate diet in newly diagnosed diabetic cats and switching to a high fiber diet if there is a poor response to the low carbohydrate diet, particularly if there are problems with weight management on the low carb diets. Commercial high fiber diets include Hills w/d, and Purina OM. Low carbohydrate diets include Hill's m/d, Purina DM, and Royal Canin DS 44 dry.

Consistency refers to the form of the diet, i.e., canned, soft-moist or dry food. Canned or dry foods are the diet of choice in diabetics since they contain predominantly complex rather than simple carbohydrates. Canned diets tend to be lower in carbohydrates than dry diets. Since complex carbohydrates require digestion before absorption, they minimize postprandial fluctuations in blood glucose concentration. Soft moist foods contain simple carbohydrates which are rapidly absorbed. These diets may result in rapid fluctuations in blood glucose 30–45 minutes after eating. Soft moist foods also contain large quantities of propylene glycol which cause postprandial hyperglycemia.

The daily caloric intake should be designed to correct obesity and maintain ideal body weight. Obesity has been shown to cause reversible insulin resistance in man due to its effects on insulin receptors. This also appears to be important in cats, in which reversal of obesity may improve or reestablish normal glycemic control. In dogs reversal of obesity may improve glycemic control and decrease the requirement for insulin, but is unlikely to replace the need for insulin therapy. The feeding schedule is also very important in diabetic patients. Feeding should occur when insulin is present in the bloodstream in order to utilize glucose as it is absorbed. If this does not happen severe postprandial hyperglycemia will occur. Also multiple feedings are preferable since this will help minimize the hyperglycemic effect of each individual meal. Ideally 3–4 small meals/day should be fed, however the schedule of most owners limits the ideal feeding schedule. For dogs receiving once a day insulin (rarely well controlled on this schedule), one meal should be given at the time of insulin administration, and a second meal given in the late afternoon at the time of peak insulin effect. For those dogs receiving insulin twice a day, at least 4 meals would be ideal. In most cases, however, two meals are fed at the same time as insulin is administered. As in every aspect of management of the diabetic patient a regular and consistent feeding schedule is the most important factor.

The same principles apply to the dietary management of diabetic cats. In obese cats or those in multi-cat households the ration should be meal fed to ensure a consistent and if necessary a calorie restricted diet. For others, allowing cats to nibble a dry ration throughout the day seems to work well.

### **ORAL HYPOGLYCEMIC AGENTS**

The sulfonylurea drug, glipizide (Glucotrol, Pfizer Inc) is the only oral hypoglycemic drug that has been appropriately evaluated for use in cats. The primary effect of glipizide is to increase  $\beta$ -cell sensitivity to insulin and increase insulin secretion. Glipizide also decreases hepatic glucose production, reverses post receptor defects, and increases the number of insulin receptors. Since functional  $\beta$  cells must be present for glipizide to be effective, one would predict that glipizide is only likely to be effective in cats with Type II DM. This is certainly the case in man, however basal insulin concentrations or glucagon tolerance tests do not appear to be useful in predicting response to treatment in the cat. Fifteen percent of cats had a good response to glipizide at a dose of 2.5–5 mg PO q 12 hours. A further 15–20 % of cats show a good clinical response to glipizide, although their blood glucose concentrations do not decrease below 200 mg/dl. The remainder show no response to the drug and require insulin therapy. There is no evidence that use of oral hypoglycemic drugs in conjunction with insulin improves glycemic control of insulin resistant cats.

Potential side effects of glipizide in humans include bone marrow depression, nausea, vomiting, dermatologic changes, cholestasis, and increased liver enzymes. The most common side effects reported in cats are hypoglycemia, vomiting, and increased hepatic enzymes. These reactions occur in less than 10 % of patients. Candidates for glipizide therapy are cats that are not ketotic, that are stable metabolically, and that are in reasonable body condition. Glipizide is administered at a dose of 2.5–5 mg PO q 12 hours in conjunction with a meal. Treatment should also include dietary therapy and correction of obesity. If treatment is effective, improvements in clinical signs and blood glucose concentrations usually occur within one month. Glipizide is discontinued and insulin therapy initiated if clinical signs continue to

worsen, the cat becomes ill or develops ketoacidosis, blood glucose concentrations remain greater than 300 mg/dl after 1–2 months of therapy, or if the owners become dissatisfied with therapy. Glipizide should also be discontinued if hypoglycemia occurs. Sometimes a lower dose of glipizide may be necessary.

The choice of therapy for an individual cat with DM depends on a number of factors including the clinical condition of the cat, and the wishes of the owner. My approach is to initially start with insulin therapy in any cat which is systemically ill at the time of diagnosis. Once the cat is more stable, a trial with glipizide can be considered if the owners prefer this approach. I often recommend a trial of glipizide if only low doses of insulin are necessary to control the diabetes. In cats that are systemically well at the time of diagnosis, glipizide therapy can be instituted first, and insulin therapy only initiated if the cat fails to respond.

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