CURRENT OPTIONS FOR INSULIN THERAPY IN DOGS AND CATS
J. Catharine Scott-Moncrieff MA, MS, Vet MB, Dipl. ACVIM (internal medicine), Dipl. ECVIM-CA

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 β-cell secretagogues such as glucagon, and is the most common form of diabetes recognized in the dog. Approximately 70% of feline diabetics also appear to have type I DM. 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 occurs in approximately 30% of diabetic cats. 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 test is of little clinical utility.

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 straightforward, 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 glycosuria, 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. Glycosuria may also occur secondary to ketamine anesthesia, chronic renal failure, and post-obstructive diuresis. 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 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, 6-15% of cats with DM were reported to go into spontaneous clinical remission, and in other studies this figure has been even higher. Although in theory only cats with Type II DM would be expected to have transient disease, both cats with Type I and Type II DM (based on the glucagon tolerance test) have been reported to have transient DM. Therefore the glucagon tolerance test is not useful in predicting whether or not a cat is likely to go into remission. Diabetes mellitus is usually permanent in dogs, 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. 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 in the past 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 current insulin products that are available are listed below:

**Insulin products currently available and recommended for use in dogs and cats**
(list does not include insulin analogues).

**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 parts semilente, seven parts ultralente)  
Mix of crystalline and amorphous in 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)  
Note that there is no longer a commercially available Ultralente insulin.  

**Insulin therapy in cats:** Insulin products that are most suitable for use in cats include Lente, and PZI insulins. PZI Vet in one study was effective in achieving glycemic control in 90% of diabetic cats. This insulin would be my first choice for use in cats, however it is expensive ($82/vial, 20c/unit). Pork Lente insulin (Vetsulin) may also be used successfully in cats and would be my second choice product. Although it is not yet licensed in the US for cats it has been used successfully for years in cats in Europe. Useful information regarding use of vetsulin in cats (called caninsulin in Europe) can be found at the website caninsulin.com. NPH insulin may also be used in the cat although it tends to have a very short duration of action and would not be my first choice. Preliminary studies of a very long acting insulin analogue (insulin Glargine®) have also been very promising.  
The starting dose for insulin in a new feline diabetic patient is 0.2 – 0.6 Unit/kg or 1-3 U/cat. It is recommended that PZI insulin is started at the lower end of this dose.  
It is difficult to predict in advance which cats will do better with which insulin formulation. The potency of different insulin formulations may vary from cat to cat, but this is not usually predictable in an individual animal, although longer acting insulins as a rule are less potent than shorter acting insulin. It is therefore important that a blood glucose curve is performed within 5-7 days of making any change in insulin formulation. Cats should also be carefully monitored for clinical signs of hypoglycemia, because of the possibility of remission of diabetes mellitus in the cat. Whatever insulin formulation is chosen, twice a day insulin therapy is most likely to result in ideal glycemic control. If this is not possible, once a day therapy with PZI Vet or Glargine can cause effective control of clinical signs.  

**Insulin therapy in dogs:** Insulin formulations are the most effective in dogs include human recombinant NPH (Humulin N) or Lente (Vetinsulin®) 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 insulin antibodies in dogs treated with beef/pork insulin. Long acting insulins such as PZI are quite unpredictable in dogs and are not appropriate for the management of most diabetic dogs.  

**Switching from one insulin product to another**  
Evaluate how well regulated the animal is on current insulin product.  
Determine potency of new insulin versus old insulin (long acting insulins are less potent than moderate acting insulins).  
Determine frequency of new insulin administration  
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.  
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. This is liable to 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.  
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 is an important adjunct therapy in management of diabetic dogs and cats  
High fiber moderately fat restricted diets are usually recommended for management of diabetic dogs. Exceptions to this are those patients for which palatability of these diets is an issue, those patients with other medical problems that might require a alternate prescription diet, and very debilitated patients in which more calorie dense diets are necessary initially. There is less agreement about dietary management of diabetic cats. Options include a high fiber, moderate carbohydrate and fat diet; or a high protein low carbohydrate diet; Which diet will be most effective in improving glycemic control in individual patients is unpredictable, although preliminary studies of a high protein low carbohydrate diet in combination with a new long acting insulin (insulin Glargine®) have been promising.
POOR RESPONSE TO INSULIN

Clinical signs suggestive of inappropriate response to insulin therapy include recurrence or persistence of clinical signs of DM, disorientation or seizures due to hypoglycemia, an insulin dose higher than 2 U/kg/dose in the dog or >6 U/dose in the cat. Adequate assessment of the cause of the problem requires performing a blood glucose curve. Measurement of glycated hemoglobin or fructosamine may also be helpful. Once this has been evaluated, appropriate changes in treatment or further diagnostic testing can then be instituted. In dogs and cats receiving twice daily insulin, most glucose curves can be performed during working hours (8 am to 6 pm). Common problems that may lead to a poor response to insulin include problems with owner administration, inappropriate insulin dose or formulation, insulin induced hypoglycemia, rapid metabolism of insulin, and insulin resistance. It is important to take into consideration the level of stress of the patient while in the hospital, when interpreting the results of blood glucose curves.

Other factors such as clinical signs, results of urine blood glucose measurements at home, serum fructosamine concentrations, and changes in physical examination (especially body weight), should be taken into account when interpreting the results.

Problems with owner administration: Diagnosis of problems with owner administration of insulin sometimes requires administration of insulin from a new bottle in the clinic by a clinician or veterinary technician. Care should be taken to monitor the patient carefully in this setting however, because severe hypoglycemia can result if the insulin dose has been escalated due to problems with administration. If hypoglycemia does occur, the dose of administered insulin should be decreased by at least 25-75 % and a blood glucose curve repeated after 7 days of the new dose.

Inappropriate insulin dose or formulation: In most cases this diagnosis can be made easily by evaluation of the blood glucose curve. Most dogs and cats require insulin administration twice daily for good glycemic control, so this is the first change to consider if inadequate insulin dose is suspected.

Insulin Induced Hypoglycemia: Insulin induced hypoglycemia (Symogi effect) occurs when excessive amounts of insulin are administered. When the blood glucose concentration drops below 65 mg/dl in response to insulin, compensatory mechanisms drive the blood glucose back into the normal range. These mechanisms include increased glycogenolysis, and gluconeogenesis by the liver, and release of catecholamines, glucagon, cortisol, and growth hormone which oppose the action of insulin. As the blood glucose returns toward normal however, there is not enough insulin present to oppose and dampen these mechanisms, and hyperglycemia may result. Since a spot-check blood glucose or urine measurement performed in the afternoon in such a case may reveal hyperglycemia and glycosuria, changes in insulin dosage based on these measurements may worsen the situation. The diagnosis of insulin induced hypoglycemia is made by performing a serial blood glucose curve. The condition is treated by decreasing the insulin dose by 25 – 75 % and reevaluation of a serial glucose curve 3 - 5 days later.

Rapid metabolism of insulin: Rapid metabolism of insulin refers to a situation when the effect of insulin does not last as long as is necessary to control hyperglycemia for the majority of the treatment period. In most diabetic dogs and cats, twice daily insulin administration is necessary for ideal glycemic control. In some cases however the duration of effect may be only 5 - 8 hours. This may mean that hyperglycemia is present for a significant proportion of the day, even when twice daily administration is instituted. In most cases clinical signs of hyperglycemia are not present and no change to therapy is necessary. In some cases an insulin preparation with a longer duration may be necessary. Alternatively three times a day insulin treatment can be considered.

Insulin Resistance: There are many varied causes of true insulin resistance, however most commonly it occurs due to the effect of excessive concentrations of hormones that oppose insulin. In many cases this is due to the presence of concurrent disease. The differential diagnosis of insulin resistance in dogs and cats is shown in the table.

Insulin resistance in dogs and cats (*most common)

<table>
<thead>
<tr>
<th>Dogs</th>
<th>Cats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug administration (progestagens/corticosteroids)*</td>
<td>Drug administration (progestagens/corticosteroids)*</td>
</tr>
<tr>
<td>Infection (urinary tract/oral cavity/sepsis)*</td>
<td>Infection (urinary tract/oral cavity/sepsis)*</td>
</tr>
<tr>
<td>Hyperadrenocorticism*</td>
<td>Hyperthyroidism*</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Impaired insulin absorption (Ultralente insulin)</td>
</tr>
<tr>
<td>Renal disease*</td>
<td>Acromegaly*</td>
</tr>
<tr>
<td>Pancreatitis*</td>
<td>Pancreatitis*</td>
</tr>
<tr>
<td>Pregnancy/diestrus*</td>
<td>Renal disease*</td>
</tr>
<tr>
<td>Pheochromocytoma/glucagonoma</td>
<td>Hepatic disease</td>
</tr>
<tr>
<td>Hepatic disease</td>
<td>Cardiac insufficiency</td>
</tr>
<tr>
<td>Cardiac insufficiency</td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Hyperlipidemia*</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Neoplasia</td>
<td>Severe obesity*</td>
</tr>
<tr>
<td>Severe obesity*</td>
<td>Anti insulin antibody excess</td>
</tr>
<tr>
<td>Exocrine pancreatic insufficiency</td>
<td>Exocrine pancreatic insufficiency</td>
</tr>
<tr>
<td>Anti insulin antibody excess (beef insulin)</td>
<td>Hyperadrenocorticism</td>
</tr>
</tbody>
</table>

REFERENCES