DIABETES MELLITUS IN CATS
As with the disease in humans, diabetes in cats (and dogs) is likely a multifactorial process. However, there are two factors that have a crucial role in determining whether or not diabetes develops, and if diabetes does occur, whether or not it is insulin dependent. The first of these determining factors is the severity of destruction of the pancreatic islets. Once islet destruction has commenced, the presence, severity, and reversibility of concurrent disorders that negatively impact insulin sensitivity (resistance factors), are the primary determinants of the cat's need for insulin. Thus, the classification of diabetic cats into Type I (insulin dependent), Type II (non-insulin dependent) or transient diabetics can be very difficult, frequently confusing, and often in error, because some cats appear to not require insulin initially, and then progress to insulin dependency later. Other cats flip back and forth between insulin dependency and not, as the severity of the impairment of beta cell function, insulin resistance, and other factors wax and wane. These apparent flip-flops are understandable when one realizes the huge variation that occurs in these three factors that are important in determining the diabetic state in cats: 1) islet pathology may be quite variable (mild to severe, static to progressive), 2) the ability of the pancreas to secrete insulin is dependent on the degree of islet pathology (which can change with time), and 3) the peripheral tissue responsiveness to insulin, which varies due to many factors (e.g. obesity, inflammatory, infectious, neoplastic or hormonal disorders). Each of these different variables can affect the need for insulin, the dose of insulin, and the overall ease of patient management.

While figures vary, recent studies indicate that greater than 25-35% of cats in the United States are overweight or obese. There are a large number of factors that contribute to this problem, including sex (intact vs. neutered, male vs. female), age, activity (outdoor vs. indoor), and feeding style (meal feeding vs free choice). However, the fact remains that obesity is a significant contributor to morbidity in middle aged to older cats. Further, as we are all aware, “it is much harder to take it off, than it is to put it on.” One factor that is increasingly being considered, both in the development of and treatment of obesity, is the role of carbohydrates (CHO) as excess calories in diet. Because of the metabolic requirement for cats to utilize protein as an energy source, CHO in the diet that are not immediately used for energy (e.g. via exercise or other utilization for energy) will be stored as fat. This is important for several reasons, but in cats, it can be a major contributing factor to development of glucose toxicity which can lead to the development of islet malfunction and ultimately, diabetes mellitus.

Cats are obligate carnivores. And, while cats can use carbohydrates (CHO) as a source of metabolic energy, they have no requirement for them (nor do dogs for that matter). But, more importantly, because cats evolved consuming prey (e.g. high protein, low to moderate fat, minimal carbohydrate), they are metabolically adapted for higher protein metabolism and lower CHO utilization. Thus, there are a number of specific metabolic and biochemical differences in feline physiology that are important, especially in the prevention or treatment of feline obesity, and possibly, diabetes.

Key Points in Carnivore Metabolism That Alter Glucose Needs/Utilization:

- Cats have an obligate need for protein and amino acids in their daily diet because they are unable to down regulate their urea cycle or transaminases (enzymes used to convert proteins into forms used for energy) as other species can in times of starvation.
- Cats continue to utilize protein for energy, even in the face of large amounts of CHO in the diet – thus, CHO in the diet is not protein or energy sparing as it is in other species.
- Utilization of dietary CHO is inefficient in cats: they lack salivary amylase, have reduced concentrations of intestinal amylases and disaccharidases, and have no fructokinases (they can’t use fructose sugars metabolically).
- Cats have greatly reduced activities of hepatic enzymes (e.g. glucokinase) designed to convert a post prandial glucose load to glycogen and thus are less able to handle large post prandial glucose loads. This is due to evolutionary pressures – they got their energy from prey (protein) and didn’t need a mechanism to digest large loads of CHO in the diet.
- In cats, amino acids and glucose, are both signals for insulin release.

THE ROLE OF AMYLIN
Amylin (or islet-amyloid polypeptide (IAPP) is the principal constituent of amyloid deposited in the pancreas of cats with diabetes. Amylin is co-secreted with insulin by beta cells, and thus any stimulants for insulin secretion also stimulate secretion of amylin. The role of this neuroendocrine peptide is believed to be as a glucoregulatory hormone counteracting the effects of insulin in the post-prandial state. However, chronic increased secretion of amylin (and insulin), as a result of obesity or other insulin resistance states (e.g. glucocorticoids, acromegaly, infection, etc), results in deposition of amylin in the islets as amyloid. Amyloid is toxic to beta cells, resulting in cell death, and thus decreased insulin secretion. If the deposition of amyloid is progressive (e.g. persistent obesity), islet cell destruction progresses and eventually leads to diabetes. It is the severity of this destruction (islet amyloid deposition) that determines (at least in part) whether the cat is insulin dependent or not. Progressive amyloid deposition leads from subclinical or transient diabetes to non-insulin dependent diabetes and finally to insulin dependent diabetes as the islet pathology progresses.

TRANSIENT DIABETES
Persistently elevated blood glucose levels also lead to development of a condition called “glucose toxicity” which is a phenomenon affecting the glucose sensing receptors on the pancreatic beta cells – the end result is a down regulation of these receptors – the beta cells simply stop responding to the glucose and stop producing insulin. The end result is development of clinical diabetes; however, if the cause for the persistent hyperglycemia can be reversed (removal of steroids, correction of obesity, treatment of hormonal disorders, etc), and the beta cells are not permanently
Key Factors in Feline Diabetes:
- Degree of islet pathology (amyloid deposition) determines to large extent whether insulin required
- Insulin resistance due to obesity is a major factor in the development of glucose toxicity from persistent hyperglycemia in cats
- Correction of glucose toxicity (reduction of CHO in diet, correction of obesity) is an important aspect of prevention of further amyloid deposition and development of permanent diabetes.

CANINE DIABETES MELLITUS
Dogs with diabetes usually have insulin dependent diabetes, so while insulin resistance can occur in dogs and contribute to poor diabetic control, non-insulin requiring diabetes is rare in dogs. The cause of diabetes in dogs is unknown, but is believed to occur due to a combination of genetic susceptibility (e.g. Keeshunds), islet destruction due to pancreatitis, concurrent hormonal disease resulting in insulin resistance (e.g. hyperadrenocorticism, diestrus induced hypersomatotropism), and immunologic destruction of beta cells. The factors that are thought to contribute to the development of antibodies against beta cells are unknown, but drugs and infectious agents are suspected. But, no matter what the inciting cause, the overwhelming majority (if not all) dogs with diabetes will require insulin to manage their disease.

DIETARY MANAGEMENT OF DIABETES MELLITUS
For all diabetics, the goals of therapy include restoration of normal fasting blood glucose concentrations, normalization of body weight (loss or gain), and reversal or attenuation of chronic complications of diabetes (UTI, cataracts, nephropathy, neuropathy, etc.). For dogs, control of their diabetes is linked to a combination of appropriate insulin therapy and dietary management that reduces post prandial hyperglycemia and maximizes insulin effectiveness. Alternatively, in cats, a combination of dietary therapy, oral hypoglycemic drugs, and insulin supplementation may all be necessary to control the disease and reverse the clinical progression. However, regardless of the type of diabetes, appropriate dietary therapy is essential to management of feline and canine diabetes and this aspect will be discussed first.

DIETARY THERAPY IN CATS
For many years, we applied similar dietary approaches in managing diabetic cats, but the data was less compelling. Recently, an approach to feeding cats, based on their strictly carnivorous nature (and physiologic adaptations), has been recommended – with excellent results. The reason for this is that most cats (including normal cats) fed typical feline diets (e.g. dry, CHO based foods) have mild, but prolonged (18-24 hr) post-prandial hyperglycemia. High protein, low carbohydrate diets (e.g. Purina DM, Hill’s m/d, all canned kiteset foods) provide protein (which the cat needs for energy, insulin stimulation, and maintenance of lean body mass), and have very low levels of CHO (to reduce postprandial hyperglycemia, and reduce excess energy from CHO). Diets with increased amounts of insoluble fiber that have been traditionally recommended for diabetic cats (e.g. Hill’s w/d) may reduce the glycemic load (by reducing absorption of
glucose in the intestine) just as they do in dogs, but may not be as effective in inducing weight loss (without loss of lean body mass) and may make cats more prone to development of constipation (due to dehydration and excessive stool dryness). However, these high fiber diets are still CHO based, so will not improve postprandial hyperglycemia like low CHO diets do. In cats with transient or non-insulin dependent diabetes, feeding the high protein/low CHO diet along with addition of an oral hypoglycemic agent (to be discussed later) may be sufficient for management of the disease. However, most cats require some insulin – even if it is just for a short time – and in this setting, high protein/low CHO diets provide a more appropriate nutrient profile, often result in reduced insulin requirements by 1/2 or more, and will normalize body condition (obese cats tend to lose weight, lean cats tend to normalize their weight). A final note on feeding diabetic cats most feline diabetics respond better to lean diets tend to normalize their weight). A final note on feeding diabetic cats most feline diabetics respond better to feeding small meals frequently (or ad libitum if they are not severely obese) as it reduces the risk of hypoglycemia and is more likely to result in more consistent blood glucose levels throughout the day.

**ORAL HYPOGLYCEMIC THERAPY (CATS)**

Indications for oral hypoglycemic therapy in cats include normal or increased body weight, lack of ketones, probable non-insulin dependent diabetes with no other underlying diseases (e.g. pancreatitis), no history of diabetogenic medications (e.g. steroids, progestagens) and the owners willingness to administer oral medications or unwillingness to administer insulin. There will be very few, if any, situations in dogs where oral hypoglycemia therapy is indicated or will result in appropriate control of their hyperglycemia. Thus, oral hypoglycemic therapy is not recommended as an alternative therapy in dogs unless the dog has shown documented evidence of having transient diabetes that is not due to diestrus, hyperadrenocorticism, or exogenous steroid use. Most cats will respond best to insulin therapy, even if they have residual beta cell function (see below), however, as many as 25% of cats with diabetes can achieve good clinical control of their diabetes with appropriate dietary therapy used in conjunction with an oral hypoglycemic agent. Despite the description of many oral hypoglycemics available on the market, the sulfonylurea, glipizide, is the only drug with well –documented effectiveness in the treatment of diabetic cats. The safest dose of glipizide is 2.5 mg/cat po every 12 hours, as higher doses may result in hepatotoxicity and vomiting. Even at the lower dose, all cats on glipizide should have periodic tests of their liver enzyme levels to assure that liver toxicity is not occurring.

**MECHANISM OF ACTION OF ORAL HYPOGLYCEMIC DRUGS**

- **Glipizide** (sulfonylureas) – insulinotropic, the only class of antihyperglycemic drug with a direct mechanism of action at the pancreatic beta cell (they increase release of insulin from the beta cell). Side effects: increased liver enzymes, hepatotoxicity, anorexia and vomiting. Recommended dose: 2.5 mg/cat po twice daily orally.
- **Metformin** (biguanides) – improves insulin sensitivity in peripheral tissues and is thus not effective in the absence of insulin. In contrast to glipizide, metformin decreases serum insulin concentrations. Because many cats develop hyperglycemia secondary to glucose toxicity, improving insulin sensitivity in peripheral tissues with metformin is likely to provide little benefit, since it has no effect on the beta cell or the hyperglycemia causing glucose toxicity. Side effects: few adverse effects are reported other than vomiting.
- **Acarbose** (alpha glucosidase inhibitor) – delay glucose absorption from the GI tract by competitively inhibiting enzymes that digest complex carbohydrates and simple sugars, thus reducing and slowing their absorption until the distal intestine. Has been used in both cats and dogs to assist post-prandial hyperglycemia and reduce the need for insulin. Side effects: flatulence and diarrhea. Suggested dose: 12.5 mg po twice daily with meal.
- **Troglitazone, Darglitazone** (thiazolidinediones) – enhance peripheral insulin sensitivity by decreasing hepatic glucose production and increasing peripheral glucose uptake. There is no effect on beta cell function or insulin release. These drugs have been studied in obese cats, but there is little or no information on their effectiveness in diabetic cats. However, if the cause of the diabetes is glucose toxicity and lack of beta cell production of insulin, these drugs are unlikely to be helpful. Side effects: few reports effects in obese cats studied, but there are no reports of its effects in diabetic cats.
- **Vanadium** - increases insulin receptor sensitivity by an unknown mechanism. A recent report suggests that concurrent use of vanadium reduced the dosage of insulin required. Suggested dose: 45 mg po once daily.
- **Chromium** – increases insulin receptor sensitivity by an unknown mechanism.

**INSULIN THERAPY IN CATS AND DOGS**

Even in cats suspected of having non-insulin dependent diabetes, short term insulin therapy using low doses (0.25-0.5 U/kg q12h) of an intermediate acting insulin is very beneficial in reducing the glucose toxicity that is causing beta cell dysfunction. In some of those cats with residual beta cell function, conservative insulin administration and high protein low CHO dietary therapy over 4-6 weeks may be sufficient to result in remission of the diabetes. These cats can then be managed long term by proper diet, correction and control of obesity, and monitoring of water intake and urine for glucosuria to assure continued remission. Thus, the mainstay of treatment of all cats with diabetes, even those suspected of having transient or non-insulin dependent diabetes is insulin. The key is to find an insulin that minimizes the number of injections required per day, while still providing adequate control of the diabetes. In addition, careful monitoring of all cats following initiation of insulin therapy is essential to help prevent life-threatening hypoglycemia, determine an appropriate insulin amount and frequency, and make appropriate adjustments in insulin therapy for cats that are transient or non-insulin dependent diabetics. Insulin for maintenance therapy of diabetes in cats (or dogs) is classified as either intermediate acting (e.g. lente or NPH) or long acting (ultra lente, PZI, or glargine). The best products for cats and dogs are either porcine or human recombinant intermediate acting insulin, as they are less likely to develop insulin antibodies than beef origin insulin,
and have more predictable results. The recommended starting dose for insulin (even PZI or ultralente) is 0.25 u/kg twice daily. Until recent data on glargine (see below) became available, intermediate acting insulins were recommended because they would provide more reliable glucose lowering — to completely control hyperglycemia (thus reducing glucose toxicity) over the 24 hour period. Further, most cats (92%) require twice daily injections of ultralente because this insulin has an inadequate or variable onset of action, or a variable duration of action. Thus, there is no benefit to the use of this insulin over NPH or lente in either dogs or cats. PZI is best used in cats for which the duration of action of lente or NPH is too short to provide effective diabetic control, or in situations where owners refuse to give twice daily injections. There are some cats that attain excellent glycemic control with PZI, but the variability in onset and duration that occurs with PZI (as with ultralente) makes it best used as alternate choice, not a first choice insulin. There are few dogs for which PZI is a good insulin choice — most dogs (94%) can be controlled on twice daily insulin, and more dogs are likely to develop hypoglycemia or be on high doses of insulin resulting in a Somogyi phenomenon on once daily insulin.

Finally, a new human insulin analogue, glargine, has been increasingly used for cats (there is some compelling data on the use of this insulin in cats) as once daily insulin. This insulin is not peak-less in cats, as it is reported to be in humans, for which it was designed as a “background” insulin to provide a continuous insulin source throughout the day. As with all long acting insulins, there is considerable variability in the onset, duration, and degree of action, but initial studies suggest that it should be given at a low dose (0.5U/kg), once daily for 3–5 days (it takes several days on this insulin before the true effect will be seen). After 3 and 7 days, a glucose curve is performed to determine its onset, duration and effectiveness in that cat — adjusting the dose downward by 0.5 U if the nadir is <200. Once the cat has been on this insulin for 7–10 days, the curve will flatten out due to its long duration and slower absorption (overlap occurs with the injections), and in some cats the dose has to be lowered again. Careful blood glucose monitoring in the first 2 weeks is necessary to prevent hypoglycemia due to its long effect. Once the cat stabilizes on the insulin (in 2–3 weeks) monitoring urine glucose or water intake (reduction of intake to less than 50 ml/kg/day) rather than a glucose curve may be possible in many cats. In one recent study, many of the newly diagnosed cats placed on glargine went into complete diabetic remission due to the excellent glucose control that was achieved.

**MONITORING IN CATS**

In most cats using intermediate acting insulin, the starting dose of 0.25-0.5 U/kg is administered and the cat is sent home for an adjustment period of 1–2 weeks. A glucose curve should be evaluated in 2–4 weeks, unless the cat develops clinical hypoglycemia during the initial adjustment period. The best means of assessing clinical control of most cats is the appearance of an active cat with normal or normalizing body weight, reduction of PU/PD and healthy appearance. Cats with a water intake of 20 ml/kg/day have excellent diabetic control (obviously this rule does not apply for cats with chronic progressive renal disease or other disorders of urine concentrating ability). Most cats with unregulated diabetes will consume > 50–75 ml/kg/day. Elevated serum fructosamine levels indicate a control problem, but not necessarily whether the insulin dose should be increased or decreased. If a cat is fractious or blood glucose curves are not possible, fructosamine concentrations may provide a marker of treatment effectiveness, but caution is still advised. The best means of determining what to do next in a cat or dog that is not under good diabetic control is a blood glucose curve, as this is only means to determine the onset of insulin action, the nadir of the blood glucose, and the duration of the insulin effect — each of these are important in determining whether it is a matter of not enough insulin, too much insulin, too short acting insulin or insulin ineffectiveness altogether. Remember: more insulin will not increase the duration, improve its onset or change it’s effectiveness resulting from poor absorption or faulty insulin.

In some cats (if not most), home monitoring of their blood glucose levels is highly desirable — partly due their stress hyperglycemia that can greatly affect glucose monitoring at hospitals, and partly due to the lack of cooperation (e.g. fractiousness) that may result from repeated blood draws in veterinary hospitals. There are a number of recent papers reporting the usefulness (and accuracy relative to peripheral blood) of marginal ear vein pricks for obtaining blood for glucose monitoring at home as one alternative. Others are examining newer technologies that can determine interstitial blood glucose levels, and thus do not require a venipuncture, prick or other method of blood collection. These methods will likely greatly improve our ability to monitor the blood glucose levels of diabetic cats (and dogs?). However, there is very good evidence that clinical response to therapy (normalization of body weight, reduction of PU/PD, and normalization of activity and general overall health remains a very effective means of assessment of clinical effectiveness of insulin therapy in cats. Blood glucose monitoring at home should only be used in conjunction with these clinical parameters to assess the response, and should not be used to make daily or frequent adjustments in insulin. Instead, are simply another means of assessment that must be taken with the whole.

Finally, urine glucose monitoring in cats can be very useful in predicting a cat that it going into diabetic remission. If the cat becomes aglucosuric, the insulin should be discontinued — if the urine remains negative, remission has occurred. However, if the glucosuria returns, the cat still requires insulin, but may need a lower dose or different insulin — both of which are best predicted by performing a serial blood glucose curve.

**MONITORING IN DOGS**

While noting clinical improvement, monitoring water intake, normalizing body weight, and monitoring urine glucose are very important in management of diabetic cats, glucose curves remain a key factor in assessment of the overall management of diabetic dogs. In general, the blood glucose curve is especially important for determining the nadir (lowest glucose reading), which is important in preventing hypoglycemia and in making adjustments in the type, amount and frequency of insulin.

**Key Guidelines for Blood Glucose Curves:**

- If the nadir is less than 60 mg/dL, or the dog shows signs of hypoglycemia, the insulin dose should be decreased by 50%.
- If the nadir is less than 100 mg/dL, or the pre-insulin blood glucose is less than 200 mg/dL, the insulin dose...
should be decreased by 20-25% (always round to the nearest whole number)

- If the nadir falls between 100-150 mg/dL, and the pre-insulin glucose is greater than 200 mg/dL, no adjustment in insulin dosage is required.
- If the nadir is greater than 150 mg/dL, and the pre-insulin glucose is greater than 200 mg/dL, the dog's insulin should be increased by 20-25%.
- Insulin resistance or insulin ineffectiveness is suggested if the blood glucose is very high (> 550-600 mg/dL) in a dog receiving insulin.

In most dogs on insulin that are not ketonuric, that have a stable body weight (not losing), and are not PU/PD (< 100 ml/kg/day on dry food), insulin adjustments should be made only in 1 U increments. The mantra “if a little is good, more is better” does not necessarily apply to insulin therapy. As in cats, urine glucose levels should not be used to determine insulin changes, but in contrast to cats, a negative urine glucose does not mean the dog has gone into diabetic remission (which is extremely rare in dogs). However, urine monitoring can be used to assess insulin overdose (e.g. impending hypoglycemia or somogyi overswing) or lack of good diabetic control resulting in ketogenesis.

References